13

Molecular Variations Based on Isosteric Replacements

CAMILLE G. WERMUTH

Si ce n'est toi c'est donc ton frère
If it isn't you, then it's your brother
Jean de La Fontaine (1621–1695) *Le loup et l'agneau*

I. History: Development of the isosterism concept 204
A. The molecular number 204
B. The isosterism concept 205
C. The notion of pseudoatoms and Grimm's hydride displacement law 205
D. Erlenmeyer's expansion of the isosterism concept 206
E. Isosterism criteria, present conceptions 206
F. The bioisosterism concept — Friedman's and Thornber's definitions 207
II. Currently encountered isosteric and bioisosteric modifications 208
A. Replacement of univalent atoms and groups 208
B. Interchange of divalent atoms and groups 209
C. Interchange of trivalent atoms and groups 209
D. Ring equivalents 211
E. Groups with similar polar effects 215
1. Surrogates of the carboxylic acid function 215
2. Surrogates of the ester function 217
3. Amides and peptides 221
4. Urea and thiourea equivalents 222
F. Reversal of functional groups 223
III. Analysis of modifications resulting from isosterism 224
A. Structural parameters 224
B. Electronic parameters 225
C. Solubility parameters 226
IV. Anomalies in isosterism 226
A. Fluorine–hydrogen isosterism 226
B. Exchange of ether oxygen and methylene group 228

THE PRACTICE OF MEDICINAL CHEMISTRY
ISBN 0-12-744640-0

V. Minor metalloids—toxic isosteres 229
A. Carbon–silicon bioisosterism 229
B. Carbon–boron isosterism 231
C. Bioisosterism involving selenium 232
References 232

The replacement in an active molecule of an atom or a group of atoms by another one presenting a comparable electronic and steric arrangement is based on the concept of *isosterism.* The term isosterism was introduced in 1919 by the physicist Langmuir[1] who was mainly interested in the physicochemical relationships of isosteric molecules. When, in addition to their physicochemical analogy, compounds share some common biological properties, the term *bioisosterism,* introduced by Friedman in 1951,[2] is used, even if the physicochemical resemblance is only vague.

I. HISTORY: DEVELOPMENT OF THE ISOSTERISM CONCEPT

The development of the concept of isosterism has its roots in the attempts to extend to entire molecules the knowledge acquired for elements, namely that two elements possesssing an identical peripheral electronic distribution also possess similar chemical properties.

A. The molecular number

Allen, in 1918, defined the *molecular number* of a compound in a similar way to the atomic number:

$$N = aN_1 + bN_2 + cN_3 + \cdots + zN_i$$

where

N = molecular number,
$N_1, N_2, N_3, \ldots N_i$ = respective atomic numbers of each element of the molecule,
$a, b, \ldots z$ = number of each element present in the molecule.

Compare ammonium and sodium cations as an example. The atomic number of nitrogen is 7 and that of hydrogen is 1. Thus the molecular number of the ammonium cation can be calculated and compared to that of the sodium ion:

	Atomic number	*Molecular number*
NH_4^+	$7 + (4 \times 1)$	11
Na^+	11	11

Possessing the same molecular number, the ammonium cation should resemble the sodium cation. This is roughly true. More generally, two compounds with identical molecular numbers present at least some similar physical properties (e.g. specific heat).

B. The isosterism concept

Independently from Allen, Langmuir in 1919[1] defined the concept of isosterism:

> Comolecules are thus isosteric if they contain the same number and arrangement of electrons. The comolecules of isosteres must, therefore, contain the same number of atoms. The essential differences between isosteres are confined to the charges on the nuclei of the constituent atoms.

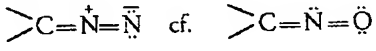
Langmuir cites a list of 21 kinds of isosteres such as

$$O^{2-}, F^{-}, Ne, Na^{+}, Mg^{2+}, Al^{3+} \quad \text{or} \quad ClO_4^{-}, SO_4^{2-}, PO_4^{3-}$$

The first example clearly demonstrates that isosterism does not inevitably imply 'isoelectric' structures (having the same total electric charge), but it becomes evident that isoelectronic isosteres show the closest analogies:

$$C{=}O \text{ and } N{=}N \qquad CO_2 \text{ and } NO_2 \qquad N{=}N{=}N^{-} \text{ and } N{=}C{=}O^{-}$$

In the field of organic chemistry, Langmuir predicted the analogy between diazomethane and ketene, which was only discovered later.



C. The notion of pseudoatoms and Grimm's hydride displacement law

Later, in 1925, Grimm formulated the 'hydride displacement law',[3-5] according to which the addition of hydrogen to an atom confers on the aggregate the properties of the atom of next highest atomic number. An isoelectronic relationship exists among such aggregates, which were named *pseudoatoms*. Thus, when a proton is 'added' to the O^{2-} ion in the nuclear sense, an isotope of fluorine is obtained (Fig. 13.1).

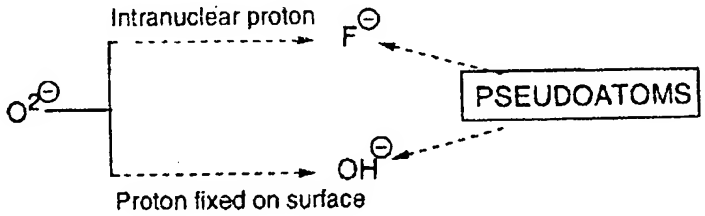


Fig. 13.1 The notion of pseudoatoms.

When the same proton is introduced at the peripheral electronic level, a 'pseudo-F', in other words an OH^{-}, is created. In this context, the H^{+} ion, having penetrated the electronic shell of the oxygen, is assumed to be masked by the greater atom and to exert only negligible effect towards the outside. The fluoride anion F^{-} and the hydroxyl anion OH^{-} therefore show some analogies. The generalization of the pseudoatom concept represents the so-called 'hydride displacement law' proposed in a tabular form by Grimm.[3,4]. In each vertical column (Table 13.1), the original atom is followed by its isosteric pseudoatoms.

Table 13.1 Hydride displacement law: in each vertical column the atom is followed by its pseudoatoms.[3-5]

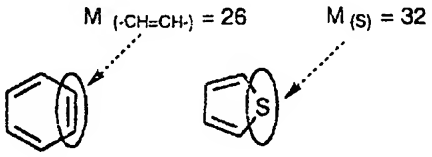
Number of electrons					
6	7	8	9	10	11
C^{4-}	N^{3-}	—O—	—F	Ne	Na^+
	CH^{3-}	—NH—	—OH	FH	
		$-CH_2-$	$-NH_2$	OH_2	
			$-CH_3$	NH_3	OH_3^+
				CH_4	NH_4^+

D. Erlenmeyer's expansion of the isosterism concept

Starting in 1932, Erlenmeyer published a series of detailed studies on the isosterism concept, and particularly about its first applications to biological problems.[6] Erlenmeyer proposed his own definition of isosteres as elements, molecules or ions in which the peripheral layers of electrons may be considered identical.[7] Erlenmeyer also proposed three expansions of the isosterism concept as follows:

1. To the whole group of elements present in a given column of the periodic table. Thus, silicon becomes isosteric to carbon, sulphur to oxygen, and so on.
2. To the pseudoatoms, with the aim of including groups that at a first glance seem totally different but which, in practice, possess rather similar properties. This is the case for the pseudohalogens, for example (Cl ≅ CN ≅ SCN, etc.)
3. To the ring equivalents: The equivalence between —CH=CH— and —S— explaining the well-known analogy between benzene and thiophene (Table 13.2).

Table 13.2 The sulphur atom is approximately equivalent to an ethylenic group (size, mass, capacity to provide an aromatic lone pair)



Compound	BP°C	Isostere	BP°C
Benzene	80°	Thiophene	84°
Methylbenzene	110°	2-Methylthiophene	113°
Chlorobenzene	132°	2-Chlorothiophene	130°
Acetylbenzene	200°	2-Acetylthiophene	214°

E. Isosterism criteria, present conceptions

The main criterion for isosterism is that two isosteric molecules must present similar, if not identical, volumes and shapes. Ideally, isosteric compounds should be isomorphic and able to co-crystallize. Among the other physical properties that isosteric compounds usually share are

boiling point, density, viscosity and thermal conductivity. However, certain properties must be different: dipolar moments, polarity, polarization, size and shape (e.g. in comparing F^- and OH^-, the size and the shape of H cannot be totally neglected). After all, the external orbitals may be hybridized differently.

In conclusion, it became evident to physicists that the concept of isosterism, developed before quantum-mechanical theories, could not provide at the molecular level the same results as those that the periodic classification had provided for the elements, namely a correlation between electronic structure and physical and chemical properties. In the field of medicinal chemistry, the isosterism concept, taken in its broadest sense, has proved to be a research tool of the utmost importance. The main reason for this is that isosteres are often much more alike in their biological than in their physical and chemical properties. An illustrative example is found in the comparison of oxazolidine-diones and hydantoins, which possess different chemical reactivities but present a similar antiepileptic profile (Fig. 13.2).

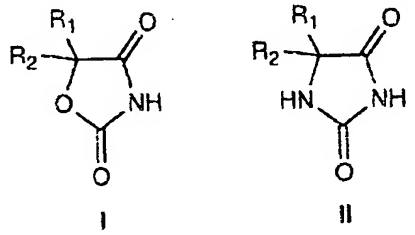


Fig. 13.2 5,5'-Disubstituted oxazolidine-diones (I) and hydantoins (II) show similar antiepileptic profiles.

F. The bioisosterism concept — Friedman's and Thornber's definitions

Recognizing the usefulness of the isosterism concept in the design of biologically active molecules, Friedman[2] proposed to call *bio*isosteres compounds 'which fit the broadest definition of isosteres and have the same type of biological activity'. This definition received rapid acceptance and is now commonly used. Moreover, Friedman considers that isosteres that exhibit opposite properties (antagonists) have also to be considered as bioisosteres, since usually they interact with the same recognition site. This is the case for *p*-aminobenzoic acid and *p*-aminobenzene sulfonamide and also for glutamic acid and its phosphonic analogues.

The use of the term isosterism has largely been taken beyond its original meaning when employed in medicinal chemistry, and Thornber[8] proposes a loose and flexible definition of the term bioisostere: 'Bioisosteres are groups or molecules which have chemical and physical similarities producing broadly similar biological effects'.

The term nonclassical isosterism is often used interchangeably with the term bioisosterism, for example, when one has to deal with isosteres that do not possess the same number of atoms but which have in common some key parameter of importance for the activity in a given series. Thus, the two GABAergic agonists isoguvacine and THIP (Fig. 13.3) possess similar pharmacological properties to GABA itself. The key parameters in these compounds are the acidic ($pK_a \approx 4$) and the basic (protonated nitrogen) functions with an intercharge distance of ≈ 5.1 Å.

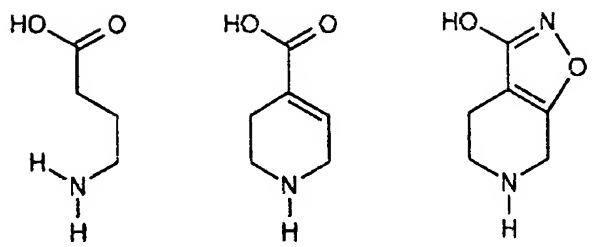


Fig. 13.3 An example of bioisosterism, or nonclassical isosterism GABA, isoguvacine and THIP are all agonists at the $GABA_A$ receptor. The 3-hydroxyisoxazole ring has a comparable acidity to that of a carboxylic acid function.[9]

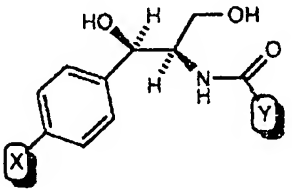
II. CURRENTLY ENCOUNTERED ISOSTERIC AND BIOISOSTERIC MODIFICATIONS

As the distinction between isosteres and bioisosteres is of rather academic interest, it is preferred, in this chapter, to treat both categories together. Consequently, divalent series such as O=, HN=, and H_2C= can be discussed together with S= for example. However, the correct nomenclature will be used as much as possible, keeping in mind, nevertheless, that 'isosteric replacement' embraces both true isosteres and bioisosteres.

A. Replacement of univalent atoms and groups

Halogens (particularly chlorine) can be replaced by other electron-attracting functions such as trifluoromethyl or cyano groups. In the antibiotic chloramphenicol, both the chlorine atoms of the dichloroacetic moiety and of the *p*-nitrophenyl group yielded productive isosteric replacements (Table 13.3). Many other examples of univalent atom or group replacements are found in the chapters dealing with substituent effects (Chapter 17) and with quantitative structure–activity relationships (Chapter 19).

Table 13.3 Isosteric replacements in the amphenicol family.

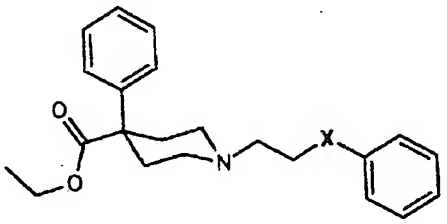


Compound	X	Y
Chloramphenicol	$-NO_2$	$-CH-Cl_2$
Thiamphenicol	CH_3-SO_2-	$-CH-Cl_2$
Cetophenicol	CH_3-CO-	$-CH-Cl_2$
Azidamphenicol	$-NO_2$	$-CH-N_3$

B. Interchange of divalent atoms and groups

A first series of frequently interchanged divalent atoms or groups is represented by O, S, NH and CH_2, and many interesting examples are found in the literature. In a study on meperidine analogues (Table 13.4) potent analgesic compounds were found for X = O, NH, and CH_2.[10] Surprisingly, the sulfur analogue showed only moderate activity. As an *in vivo* test was used to assess the activity, the weaker effect may be attributable to a faster metabolism (sulfoxide or sulfone formation?).

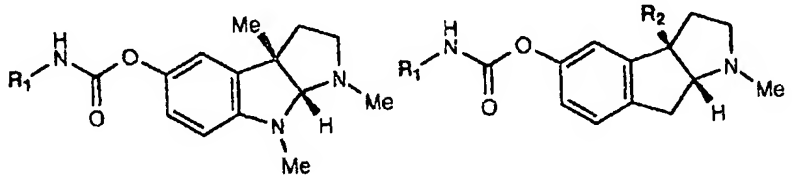
Table 13.4 Meperidine analogues.[10]



X	Analgesic potency (meperidine = 1)
O	12
NH	80
CH_2	20
S	1.5

Similar changes can be applied to cyclic series, for example to a series such as piperidine–morpholine–thiomorpholine–piperazine, or in introducing oxygen or sulfur atoms into cyclic ketoprofen analogues.[11]

Table 13.5 Physostigmines (left) and carbaisosteres (right).[12]



Compound	R_1	R_2	IC_{50} (nM)	LD_{50} (mg/kg)
(−)-Physostigmine	CH_3	CH_3	128	0.88
(−)-Heptyl physostigmine	n-C_7H_{13}	CH_3	110	24
(±)-Carba-isostere 1	n-C_7H_{13}	CH_3	114	21
(−)-Carba-isostere 2a	n-C_7H_{13}	C_2H_5	36	6
(+)-Carba-isostere 2b	n-C_7H_{13}	C_2H_5	211	18

With the objective of designing a more stable analogue of the acetylcholinesterase inhibitor alkaloid physostigmine, Chen *et al.*[12] prepared some 8-carba isosteres of physostigmine (Table 13.5). The authors envisaged that replacing the *N*-methyl group at N8 of the physostigmine nucleus by a methylene group would increase its chemical and metabolic stability, thanks to the change of the less stable aminal group to a more stable amino group.

The carba isosteres are as potent or more potent than the corresponding physostigmines. In addition, the (−)-enantiomers, which possess the same absolute configuration at C3a and C8a as that of physostigmine are generally 6 to 12 times more potent in inhibiting acetylcholinesterase than the corresponding (+)-enantiomers.

C. Interchange of trivalent atoms and groups

The substitution of −CH= by −N= in aromatic rings has been one of the most successful applications of classical isosterism (see following section on ring equivalents). Aminopyrine and its isostere are about equally active as antipyretics[13] (Fig. 13.4). Similar interchanges are found in proceeding from desipramine to nortriptyline and protriptyline (Fig. 13.4) or among the antihistaminics, when comparing ethylenediamine derived compounds to the diarylpropylamines (Fig. 13.4).

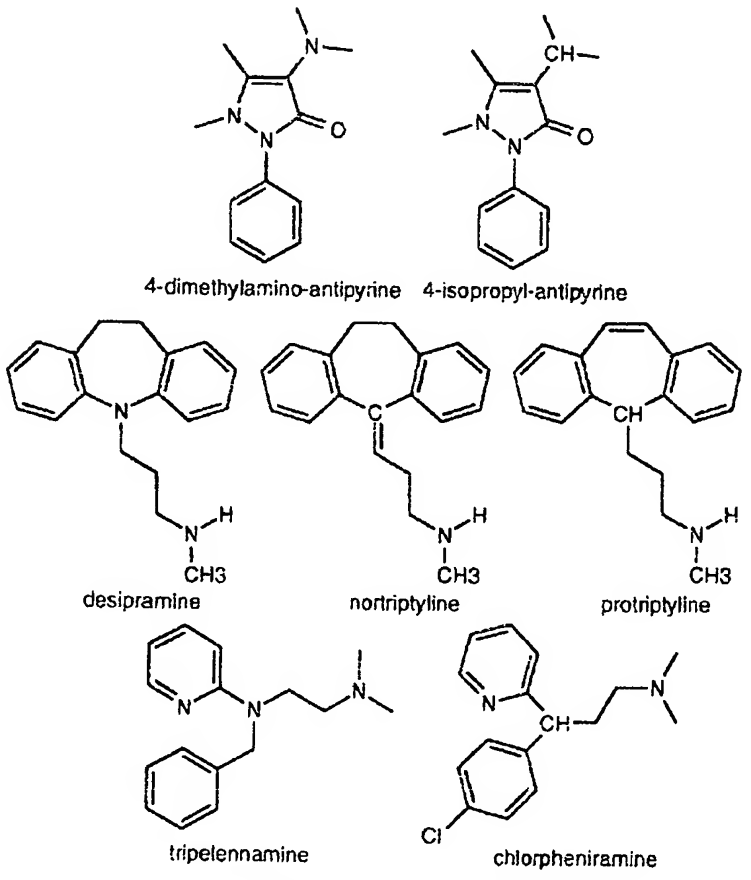


Fig. 13.4 Interchange of trivalent atoms and groups.

D. Ring equivalents

The substitution of $-CH=$ by $-N=$ or $-CH=CH-$ by $-S-$ in aromatic rings has been one of the most successful applications of classical isosterism. Early examples are found in the sulfonamide antibacterials with the development of sulfapyridine, sulfapyrimidine, sulfathiazole, etc. (Fig. 13.5).

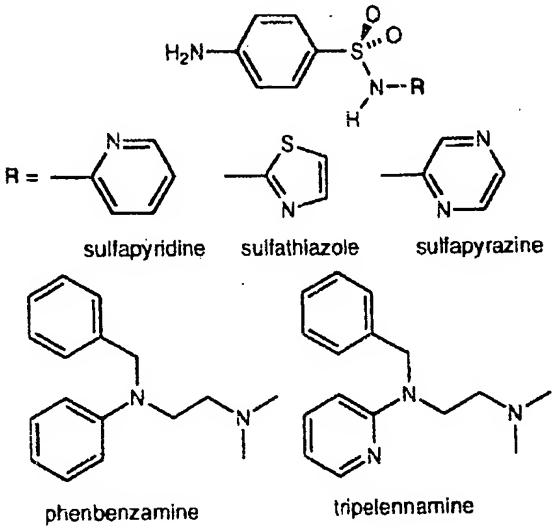


Fig. 13.5 Classical ring equivalents.

Other examples are found in the neuroleptic or antidepressant tricyclics, in the benzodiazepine tranquillizers and antiepileptics, and in the development of semisynthetic penicillins and cephalosporins with broader spectra of activity and greater stability towards β-lactamases.

In all these cases no *essential* activity difference is found between the original drug and its isostere. However, it can happen that the procedure fails. Binder *et al.*[14] for example, reported that thieno[2,3-*d*]isoxazole-3-methanesulfonamide, the thiophene analogue of the anticonvulsant drug zonisamide (Fig. 13.6),[15] was practically inactive against pentetrazole- or electric shock-induced convulsions in mice, even at high doses.

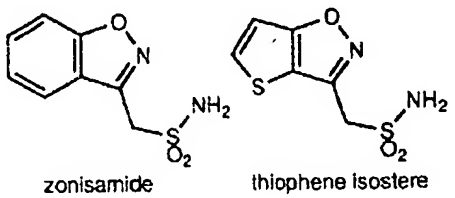


Fig. 13.6 The thiophene isostere of zonisamide is practically inactive as an anticonvulsant.

The concept of ring equivalents has been generalized to any possible heterocyclic system and represents a huge number of possible variations. Table 13.6 lists some less well-known studies on ring equivalents in aromatic series.

Table 13.6 Ring equivalents.

Original ring	Bioisostere	Activity	Reference
1-Phenylpyrazolone	1-Phenyltriazolone	Analgesic	Gold-Aubert *et al.*[16]
1,2,4-Triazole	1,3-Thiazole imidazole	Antiviral	Alonzo *et al.*[17]
Indole	Indazole	5-HT3 antagonists	Fludzinski *et al.*[18]
3,4-Dialkoxyphenyl	Indole	Phosphodiesterase inhibitors	Blaskó *et al.*[19]
3,4-Dialkoxyphenyl	Indole	GABA uptake inhibitors	Kardos *et al.*[20]
Quinoline-2-carboxylate	Indole-2-carboxylate	Glycine antagonists	Salituro *et al.*[21]
o-Nitrophenyl	Furoxane	Calcium antagonist	Calvino *et al.*[22]
spiro-Hydantoin	*spiro*-Hydroxyacetic acid unit	Aldose reductase inhibitor	Lipinski *et al.*[23]

Another particularly impressive example of ring bioisosterism is found in the development of the antiulcer H_2-receptor histamine antagonists in which the initial imidazole ring was changed to various other 'equivalents' such as a furan, a thiazole and finally a phenyl ring (Fig. 13.7). A detailed and very interesting account of the discovery and the development of these compounds is found in Ganellin and Roberts' book.[24]

One of the major problems when dealing with isosteric or bioisosteric replacements in *heterocyclic systems* is the selection of the *a priori* most promising candidate among several dozens of possible rings. A simple clue can be the knowledge and the comparison of the boiling points of the basic heterocycles. Thus, in the search for an ideal surrogate of the pyridazine ring, the comparison of the boiling points of seven possible ring candidates (Fig. 13.8), led us to reject the isomeric pyrimidine ring and to select the 1,2,4-triazine and the 1,3,4-thiadiazole rings.[25] Effectively, the observed biological activities were at least partially in accordance with the boiling point selection criteria (Table 13.7). On the reserpine ptosis and the 5-HT potentiation tests, the closest activities result from the replacement of the pyridazine ring (BP=208°C) by the 1,3,4,-thiadiazole (BP=204–205°C) or the 1,2,4-triazine (BP=200°C) ring. The pyrazine- and the pyrimidine-derived analogues are clearly less active on these two tests. The attenuation of the turning behaviour, after unilateral intrastriatal injection of the compounds in 6-hydroxydopamine-lesioned mice, reflects the dopaminergic properties of the molecules. Apparently these properties are insensitive to the bioisosteric variations.

A possible interpretation of these results could be the fact that in the heterocyclic series the boiling point is correlated to the dipolar moment of the molecule and that, for two heterocyclic rings having the same aromatic geometry, the similarity of the dipolar moments may represent the dominant feature.

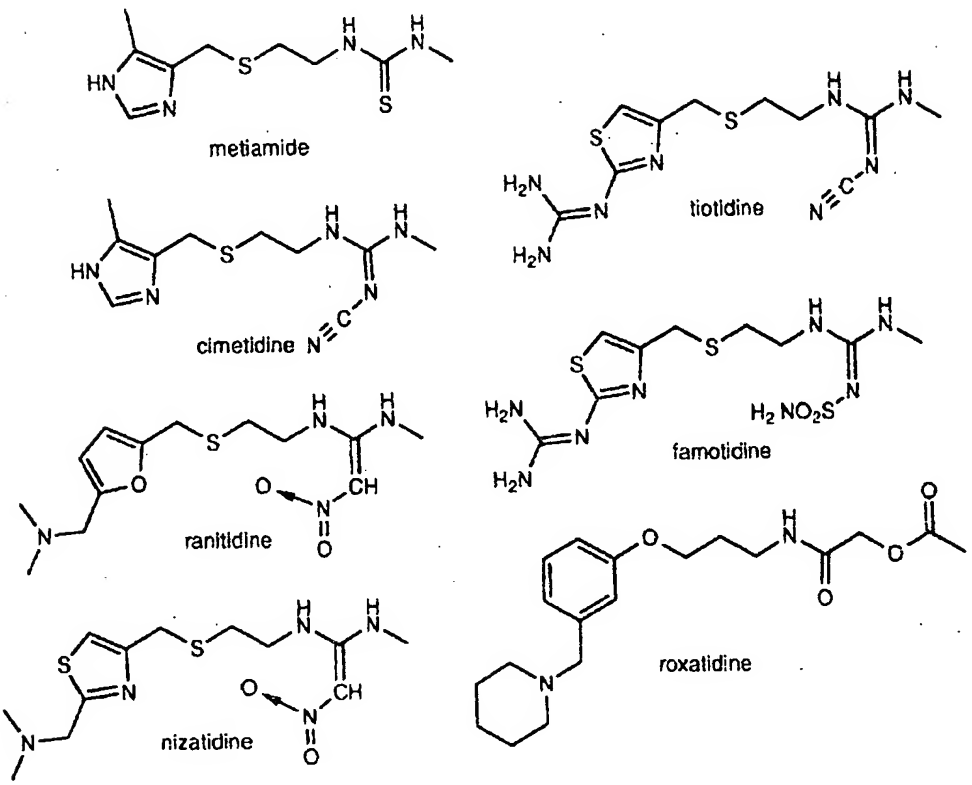


Fig. 13.7 Antiulcer H_2-receptor histamine antagonists: evolution of structures in the course of the time. Note the progressive use of a furan, a thiazole, and finally a phenyl ring in place of the original imidazole ring.

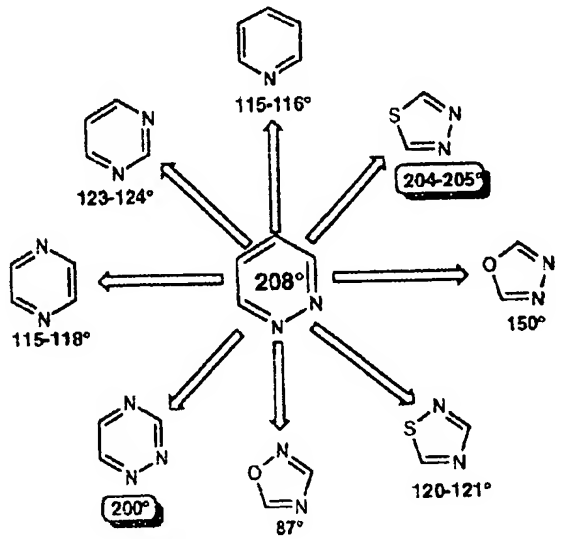
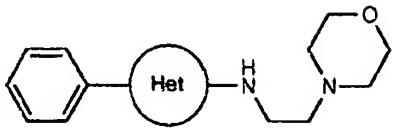
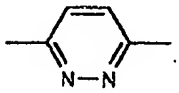
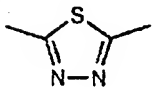
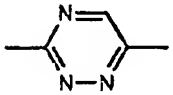
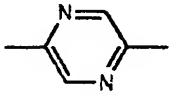
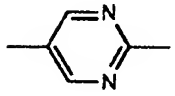


Fig. 13.8 Structure and boiling points of pyridazine isosteres.

Table 13.7 Cyclic equivalents of the pyridazine ring.[25]



Central heterocycle	Reserpine ptosis (ED_{50})	5-HT potentiation (ED_{50})	Turning (minimal effective dose)
	6	3.7	0.5
	4.5	6	0.1
	>10	6	2
	24	30	0.1
	>100	>50	2

Better bioisosteric design possibilities are provided by quantum chemical calculations. Mallamo *et al.*[26] made use of electrostatic potential surface maps complementarity in defining sulfonyl heterocycles bioisosteric to the steroidal antiandrogenic drug zanoterone (Fig. 13.9). Striking differences in the electrostatic potential surfaces accounted for the observed variability in the furan (active) and the thiophene (inactive) analogues of zanoterone (which contains a pyrazole ring). Good androgen receptor affinity was then anticipated—and effectively found—for the oxazole and the thiazole analogues of zanoterone.

The apparent failure of the isosterism concept for the inactive thiophene, inverted furan and pyrimidine is thus interpretable on a rational basis.

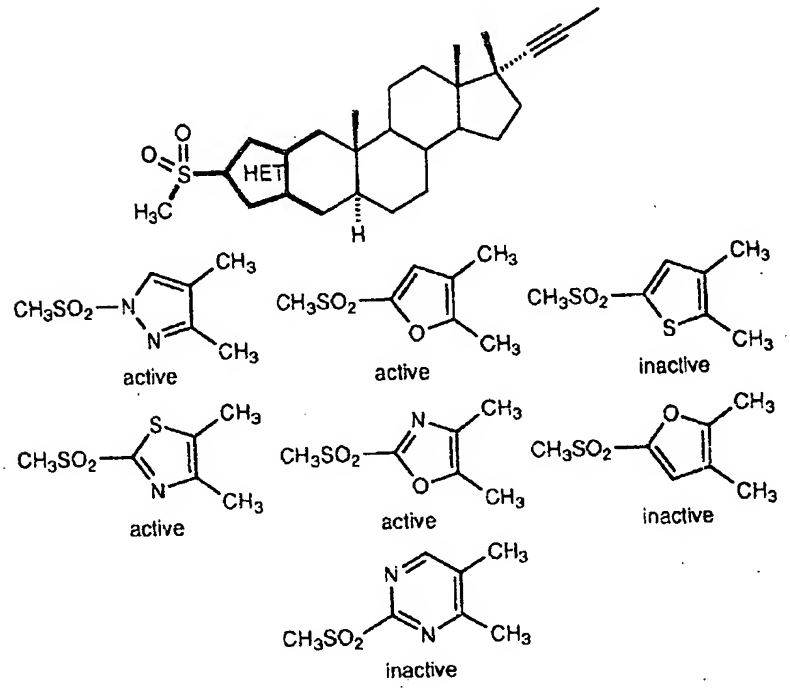


Fig. 13.9 Zanoterone isosteres.[26]

E. Groups with similar polar effects

1. *Surrogates of the carboxylic acid function*

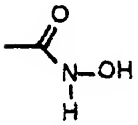
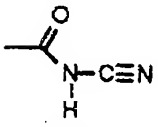
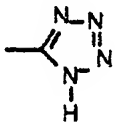
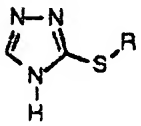
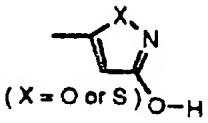
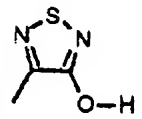
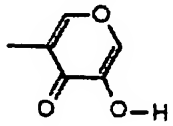
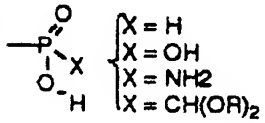
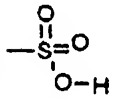
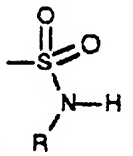
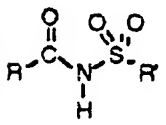
The carboxylic function of active compounds has been changed to direct derivatives such as hydroxamic acids (R—CO—NH—OH), acylcyanamides (R—CO—NH—CN) and acylsulfonamides (R—CO—NH—SO_2—R′; to planar acidic heterocycles such as tetrazoles, hydroxyisoxazoles, etc. or even to nonplanar sulfur- or phosphorus-derived acidic functions (Table 13.8).

Direct derivatives comprise hydroxamic acids[37–41], acylcyanamides[28,42] and acylsulfonamides[35] in which an acidic NH group replaces the acidic OH group. These bioisosteres are mainly of academic interest. Exception are the anti-inflammatory hydroxamates bufexamac,[37] ibuproxam,[38] and oxametacin[39,43] (Fig. 13.10). While ibuproxam is metabolized to ibuprofen (CONHOH → COOH) in man,[44] oxametacin is metabolically stable in man and is a true bioisostere rather than a prodrug.[45,46]

Among the planar acidic heterocycles the main representatives are tetrazoles and 3-hydroxyisoxazoles. The medicinal chemistry of tetrazoles has been reviewed[47] and recent examples are found in various domains.[21,29,30,48] Tetrazole surrogates have the broadest field of applications, they can increase potency,[29,30] improve bioavailability[48,49] or bring some selectivity (the GABA tetrazole analogue inhibits GABA-transaminase, but not succinic semialdehyde dehydrogenase.[50] However, in some instances tetrazole analogues are poorly active.[51]

Hydroxyisoxazoles and other cognate heterocyclic phenols encompassing an acidity range

Table 13.8 Carboxylic acid isosteres.

	Hydroxamic acids	High chelating power	Almquist *et al.*[27]
	Acyl-cyanamides	Mainly academic interest	von Kohler *et al.*[28] Shirota *et al.*
	Tetrazoles	Very popular Great number of publications. Recent in use. pK_a = 6.6 to 7.2	Bovy *et al.*[29] Marshall et al.[30]
	Mercaptoazoles + sulfinylazoles + sulfonylazoles	Phosphonate isosteres pK_a mercapto: 8.2–11.5 pK_a sulfinyl: 5.2–9.8 pK_a sulfonyl: 4.8–8.7	Chen *et al.*[12]
	Isoxazoles Isothiazoles	GABA and glutamic acid analogues	Krogsgaard-Larsen *et al.*[9] Krogsgaard-Larsen[31]
	Hydroxythiadiazole	Isoxazole isostere $pK_a \sim 5$	Lunn *et al.*[32]
	Hydroxychromes	Kojic acid derivatives: as GABA agonists	Atkinson *et al.*[33]
	Phosphinates Phosphonates Phosphonamides	Many examples in the glutamate antagonist series and in the $GABA_B$ antagonists	Froestl *et al.*[34]
	Sulphonates	Sulphonic analogues of GABA and glutamic acid	Rosowsky *et al.* (1984)
	Sulphonamides	Weak acids, used rather as equivalents of phenolic hydroxyls: catecholamine analogues	von Kohler *et al.*[28]
	Acylsulphonamides	Glycine GABA β-alanine antiatherosclerotics $pK_a \sim 4,5$	Drummond and Johnson[35] Albright *et al.*[36]

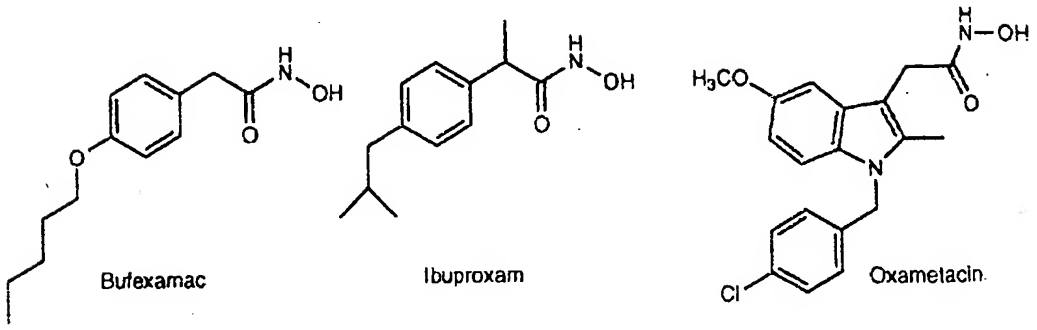


Fig. 13.10 Hydroxamate isosteres of anti-inflammatory drugs.

from 3.0 to 7.1 were incorporated in GABA agonists, antagonists and uptake inhibitors.[52,53] The experience gained with 3-hydroxyisoxazoles in the GABA field was also transferable to glutamate receptor ligands and led to selective antagonists for glutamic acid receptor subtypes.[54]

Other interesting but less studied heterocyclic surrogates are 3,5-dioxo-1,2,4-oxadiazolidine,[55] 3-hydroxy-1,2,5-thiadiazoles[32] and 3-hydroxy-γ-pyrones.[33,56]

Non planar sulfur- or *phosphorous-derived acidic functions:* The most extensive use of phosphonates was made in the design of amino acid neurotransmitter antagonists such as glutamate[57] and $GABA_B$ antagonists.[34]

In a series of CCK antagonists derived from the nonpeptide CCK-B selective antagonist CI-988, Drysdale *et al.*[58] prepared a series of carboxylate surrogates spanning a pK_a range of <1 (sulfonic acid) to >9.5 (thio-1,2,4-triazole). The affinity and the selectivity of the compounds were rationalized by consideration of the pK_a values, charge distribution, and geometry of the respective acid mimics (Table 13.9).

Diaminocyclobutenedione, was proposed by Kinney *et al.*[59] as an original surrogate of the α-amino carboxylic acid function (Fig. 13.11).

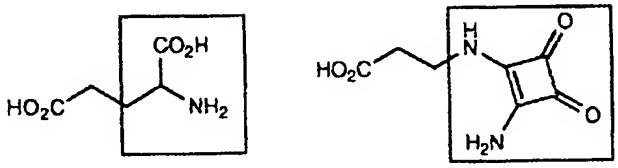
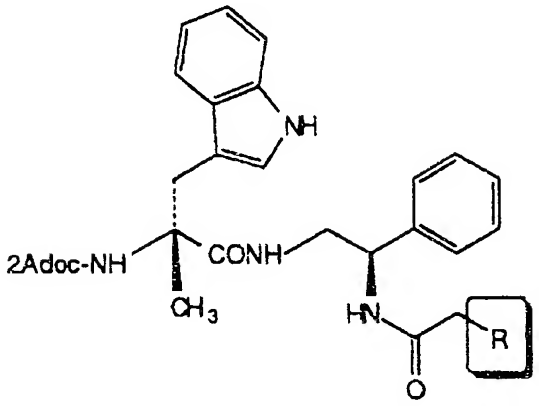


Fig. 13.11 3,4-Diamino-3-cyclobutene-1,2-dione as surrogate of the α-amino carboxylic acid function.[59]

2. Surrogates of the ester function

The change from ester to amide (procaine→procainamide) was already illustrated above as an example of classical isosterism. Similarly, the lactone ring of the muscarinic agonist pilocarpine was changed into various, still active, isosteres such as the corresponding thiolactone, lactam, lactol, and thiolactol.[60] A series of aspirin isosteres has been prepared by replacing the carboxylic ether oxygen successively by a nitrogen, sulfur or carbon isosteric equivalent.[61] None of the isosteric compounds showed any activity. This result is readily understood since the particular role of aspirin as an acylating agent of the enzyme cyclooxygenase has been demonstrated.[62]

Table 13.9 Exploration of the carboxyl isosterism possibilities in a series of CCK antagonists[58]



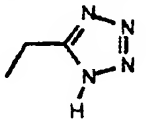
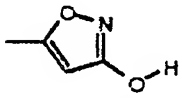
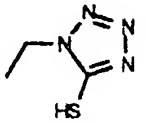
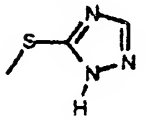
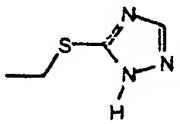
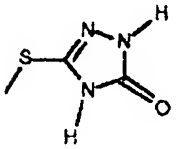
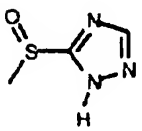
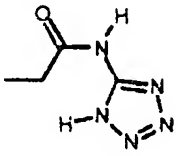
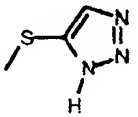
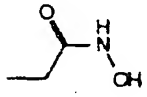
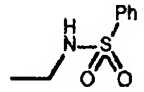
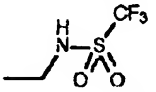
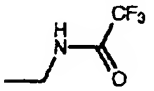
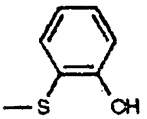
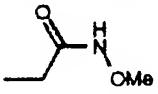
R	IC_{50} (nM) CCK-B	IC_{50} (nM) CCK-A	A/B ratio	pK_a
$-CH_2-COOH$	1.7	4500	2500	5.6
Charge-distributed monoanionic acid mimics				
	6.0	970	160	5.4
	2.6	1700	650	6.5
	2.4	620	260	4.3
	2.5	680	270	>9.5
	16	850	53	>9.5
	4.3	660	150	7.7
	1.7	940	550	7.0

Table 13.9 — *Continued*

R	IC_{50} (nM) CCK-B	IC_{50} (nM) CCK-A	A/B ratio	pK_a
	6.3	1300	200	5.2
	18	600	33	>8.2
	14	1300	93	>9.5
Point-charge monoanionic acid mimics				
	70	300	4.3	>9.5
	77	680	9	7.9
	110	790	7	>9.5
	80	510	6.4	>9.5
	21	1500	71	>9.5
Tetrahedral acid mimics				
$P(O)(OH)_2$	27	5200	190	3.4; 7.7
$CH_2-P(O)(OH)_2$	23	2700	120	3.4; 7.8
P(O)(OH)(OEt)	12	480	40	6.5
P(O)(OH)Me	12	1700	140	3.8
$CH_2-P(O)(OH)Me$	23	4400	190	3.7
CH_2-SO_3Na	1.3	1010	780	–

In addition to these classical changes, much use was made of 1,2,4-oxadiazoles or 1,2,4,-thiadiazoles as carboxylic ester surrogates in series of benzodiazepine and muscarinic[63,64] receptor ligands (Fig. 13.12). For muscarinic agonists, numerous successful attempts to replace the oxadiazole ring by other heterocyclic ring systems have been published.[65–67] By substituting in pilocarpine the lactonic ester function by its carbamate equivalent, a much more stable analogue was obtained (See Chapter 38).

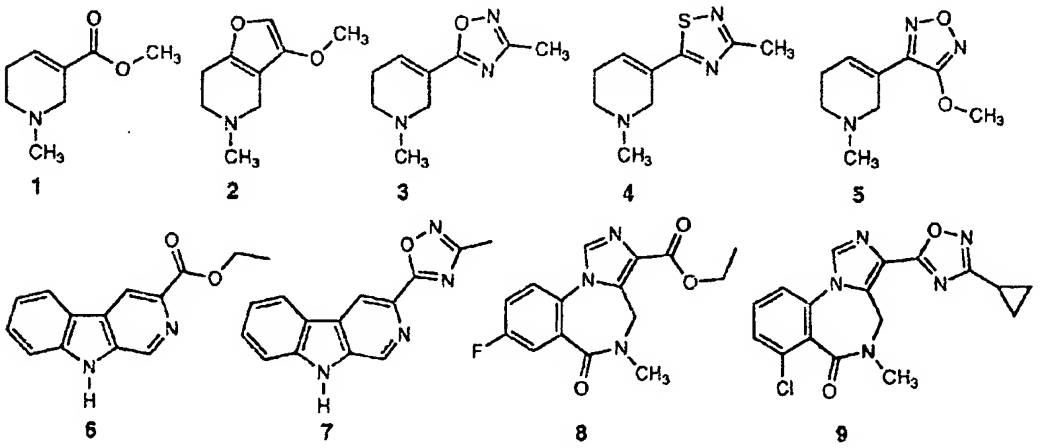


Fig. 13.12 1,2,4-Oxadiazoles and related five-membered heterocycles as ester surrogates.

The change in (−)-cocaine of the carbomethoxy substituent into carbethoxyisoxazole doubles the potency in [^{3}H]mazindol binding and [^{3}H]dopamine uptake. Astonishingly, the replacement of the carbomethoxy group by a chlorovinyl moiety produces a comparable gain in potency, thus arguing against the involvement of the carbomethoxy group in H-bonding[68] (Fig. 13.13).

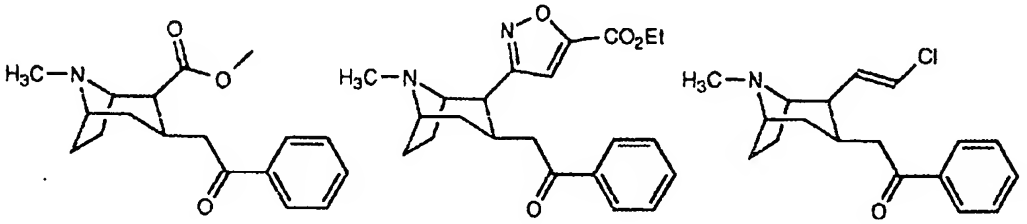


Fig. 13.13 Replacement in (−)-cocaine of the carbomethoxy group by a carbethoxyisoxazole and a chlorovinyl moiety.

Another rather unusual example of ester isosterism is the replacement of the ether oxygen by a fluoronitrogen (Fig. 13.14a) as mentioned by Lipinski.[69] Other uncommon examples are found in the replacement of the ester function of acetylcholine by exo–endo amidinic functions of 3-aminopyridazines in muscarinic agonists (Fig. 13.14b)[70] and of the carbomethoxy group of α-yohimbine (rauwolscine) by an *N*-methylsulphonamide function (Fig. 13.14c).[71]

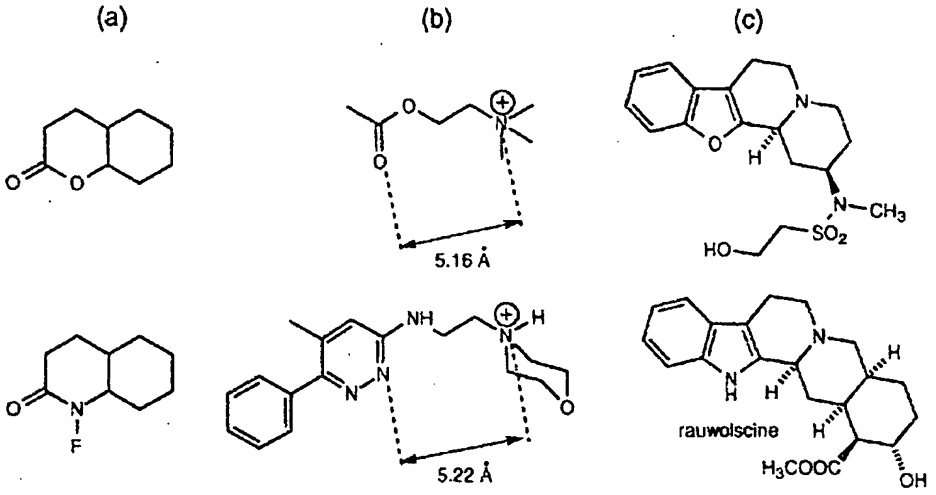


Fig. 13.14 (a) Replacement of ester ether oxygen by a fluoronitrogen. (b) Exo–endo amidine in place of a carboxylic ester functionality. (c) *N*-Methylsulphonamide analogue of α-yohimbine (rauwolscine).

3. *Amides and peptides*

Carboxamides are usually converted to sulphonamides as illustrated by the synthesis of the hypoglycaemic sulphonyl isostere of glybenclamide.[72] The isosteric replacements for peptidic bonds have been summarized by Spatola[73] and by Fauchère.[74] The most used and well-established modifications are *N*-methylation; configuration change (D-configuration at Cα); formation of a retroamide or an α-azapeptide; use of aminoisobutyric or dehydroamino acids; replacement of the amidic bond by an ester (depsipeptide), ketomethylene, hydroxyethylene or thioamide functional group; carba replacement of the amidic carbonyl, and use of an olefinic double bond (Fig. 13.15).

More unusual isosteric replacements for the peptidic bond were recently proposed. Among these, hydroxyethylureas served in the design of a novel class of potent HIV-1 protease inhibitors, diacylcyclopropanes in the design of novel renin inhibitors, and pyrroline-3-ones for various proteolytic enzyme inhibitors.[75,76] Vinyl fluorides can probably be considered as representing the closest possible bioisosteres of the peptide bond. The synthetic methods available allow, by an appropriate selection of the precursors, the preparation of analogues of dipeptidic combinations of amino acids bearing no other functionalities in their side-chains, e.g. Gly, Ala, Val, Phe, Pro.[77] Vinyl fluorides have been used in the design of bioisosteres of Substance P[76] and of the analgesic dipeptide 2,6,-dimethyl-L-tyrosyl-D-alanine-phenylpropionamide.[78]

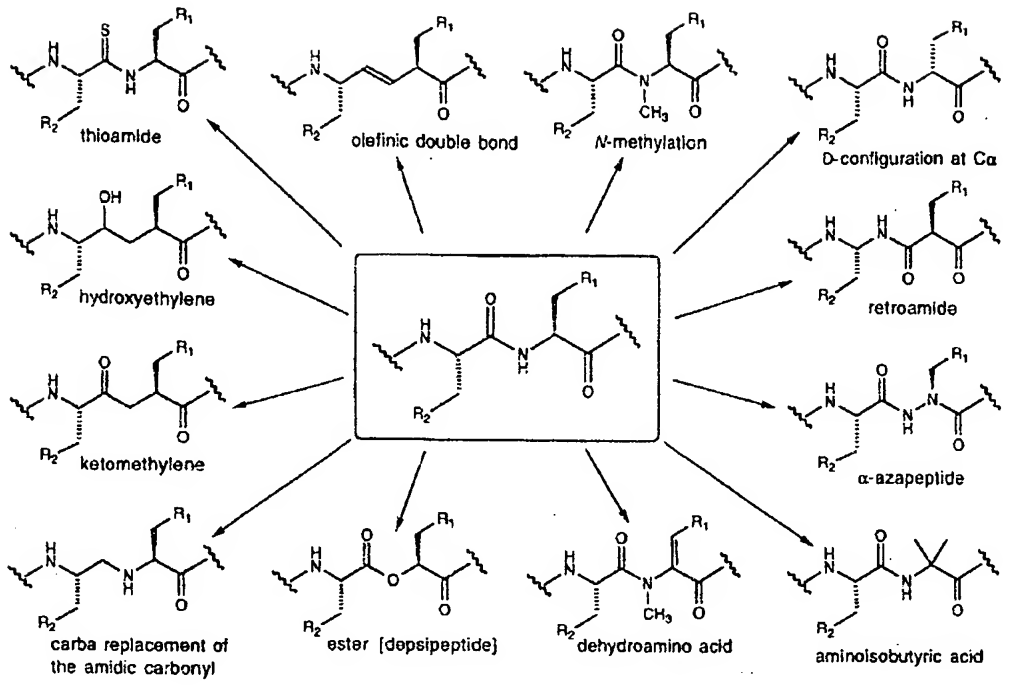


Fig. 13.15 Well-established isosteric replacements for peptidic bonds.[73,74]

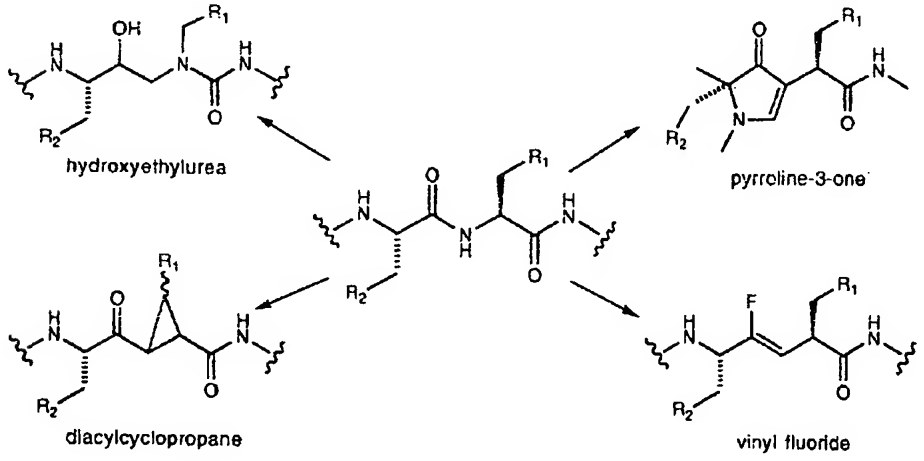


Fig. 13.16 Unusual isosteric replacements for peptidic bonds.

4. *Urea and thiourea equivalents*

In the histaminic H_2 receptor antagonist series, the classical urea–thiourea–guanidine progression was successfully completed by the use of the *N*-nitro- and *N*-cyanoguanidines and, later, by 1,1-diamino-2-nitroethylene groups[24] (Fig. 13.17). Cyano amidines and carbamoyl amidines were also used,[79] and structure–activity relationship patterns were rationalized in terms of dipole moment orientation of related bioisosteric groups.[80]

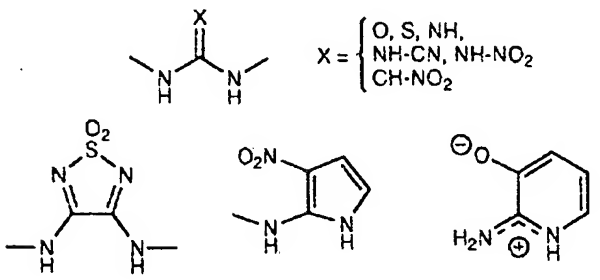


Fig. 13.17 Urea and thiourea equivalents.

Among more exotic surrogates, the 3,4-diamino thiadiazole dioxide moiety was proposed as a weakly acidic urea equivalent[81] as well as exo–endo amidinic heterocyles bearing an electron-attracting function in the α position[82,83] (Fig. 13.17).

F. Reversal of functional groups

The reversal of the peptidic functional groups is often used in peptide chemistry. The retropeptides obtained are generally more resistant to enzymatic attacks (Fig. 13.15).[74,84] But the strategy of functional inversion can also be applied to nonpeptidic compounds. A historical example is the change from orthoform to neo-orthoform (orthocaine; Fig. 13.18). The unwanted side-effects, often encountered with aromatic *p*-amino substituted compounds ('*para* effects', essentially of allergic origin) are abolished in the *m*-amino isomer, whereas the local anaesthetic activity is maintained. Similarly the '*meta*' isomer of benoxinate has a local anesthetic activity identical to that of benoxinate itself.[85]

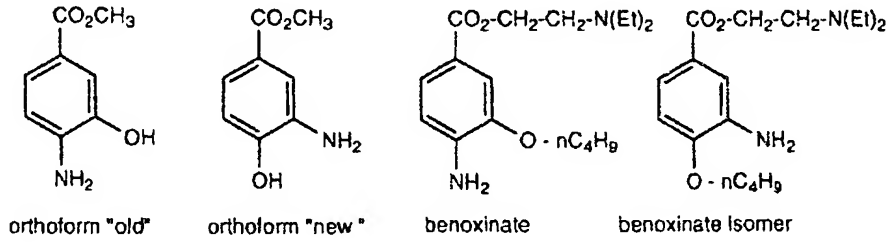


Fig. 13.18 Positional isomery in local anaesthetics.[85]

The inversion of the ester function of meperidine leads to 1-methyl-4-phenyl-4-propionoxy piperidine (Fig. 13.19) which is five times more potent as an analgesic drug than meperidine and represents the model compound of the series of inverted esters.[10]

The change from indomethacin to clometacin, although representing a clean example of functional group reversal, causes more profound alterations than that shown in the previous examples. At a first glance, this change can even seem too drastic, however, in turning the molecule of clometacin by 180°, the resemblance with the parent molecule becomes evident. Indomethacin is mainly used as a nonsteroidal anti-inflammatory agent and occasionally as an analgesic; clometacin, on the other hand, is usually recommended as an analgesic and shows weak anti-inflammatory properties.

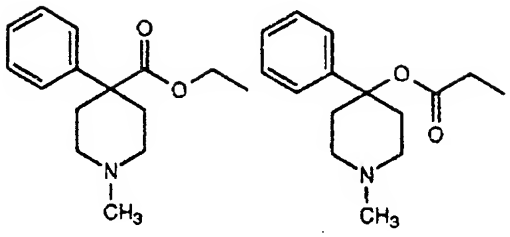


Fig. 13.19 Meperidine and the corresponding inverted ester.[10]

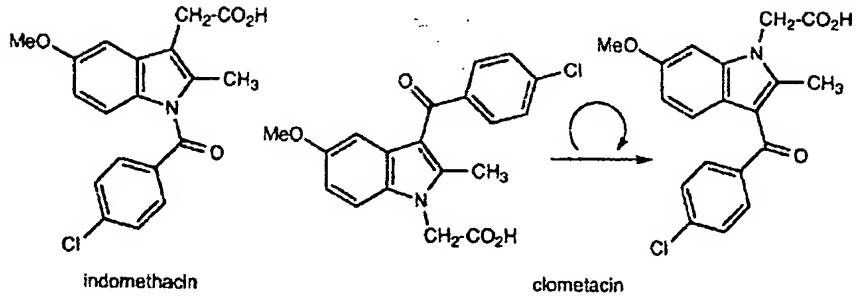


Fig. 13.20 Functional inversion applied to indomethacin.

III. ANALYSIS OF MODIFICATIONS RESULTING FROM ISOSTERISM

It is rare that the replacement of a part of a molecule by an isosteric or bioisosteric group leads to a *strictly identical* active principle. In practice, that is not even sought, and one prefers that the new compound produces a change compared with the parent molecule. In general the isosteric replacement, even though it represents a subtle structural change, results in a modified profile: some properties of the parent molecule will remain unaltered, others will be changed. Bioisosterism will be productive if it increases the potency, the selectivity and the bioavailability, or decreases the toxicity and undesirable effects of the compound. In proceeding to isosteric modifications one will focus *predominantly* on a given parameter (structural, electronic, hydrophilic) but it is all but impossible not to alter several parameters simultaneously.

A. Structural parameters

These will be important when the portion of the molecule involved in the isosteric change serves to maintain other functions in a particular geometry. This is the case for tricyclic psychotropic drugs (Fig. 13.21). In the two antidepressants (imipramine and maprotiline), the bioisosterism is geometrical insofar as the dihedral angle α formed by the two benzo rings is comparable:

α=65° for the dibenzazepine and α=55° for the dibenzocycloheptadiene.[86] This angle is only 25° for the neuroleptic phenothiazines and the thioxanthenes. In these examples the part of the molecule modified by isosterism is not involved in the interaction with the receptor. It serves only to position correctly the other elements of the molecule.

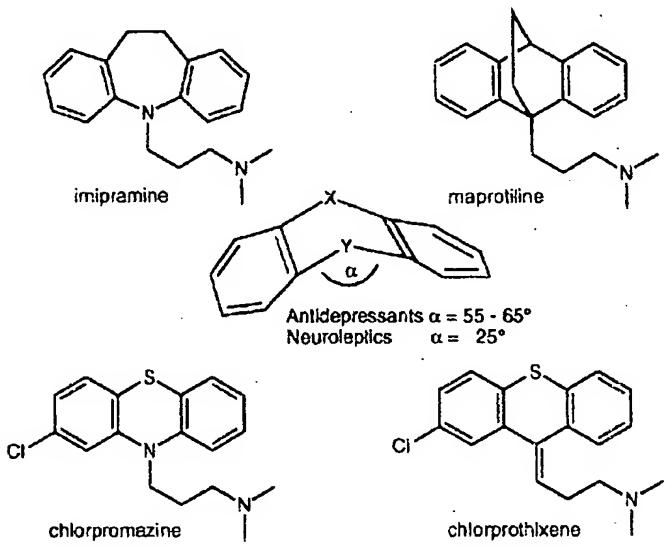


Fig. 13.21 The tricyclic antidepressants (imipramine and maprotiline) are characterized by an dihedral angle of 55–65° between the two benzo rings; this angle is only 25° for the tricyclic neuroleptics (chlorpromazine, chlorprothixene).[86]

B. Electronic parameters

Electronic parameters govern the nature and the quality of ligand–receptor or ligand–enzyme interactions. The relevant parameters will be inductive or mesomeric effects, polarizability, pK_a, capacity to form hydrogen bonds, etc. Despite their very different substituents in the *meta* position, the two epinephrine analogues (Fig. 13.22) exert comparable biological effects: they are both β-adrenergic agonists. In fact the key parameter resides in the very close pK_a values.[87]

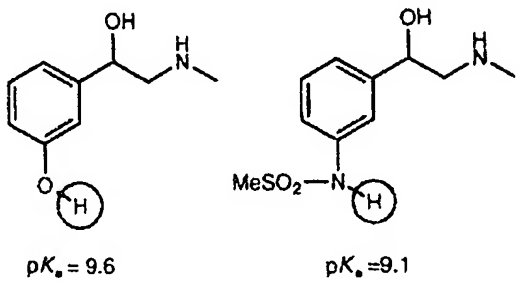


Fig. 13.22 An example of bioisosterism, or nonclassical isosterism; the methylsulphonamide substituent has comparable acidity to the phenolic hydroxyl group.[76]

C. Solubility parameters

When the functional group involved in the isosteric change plays a role in the absorption, the distribution or the excretion of the active molecule, the hydrophilic–lipophilic parameters become important. Imagine in an active molecule the replacement of $-CF_3$ by $-CN$ (Fig. 13.23). The electron-attracting effects of the two groups will be comparable, but the molecule with the cyano function will clearly be more hydrophilic. This loss in lipophilicity can then be corrected in attaching elsewhere on the molecule a propyl, isopropyl or cyclopropyl group.

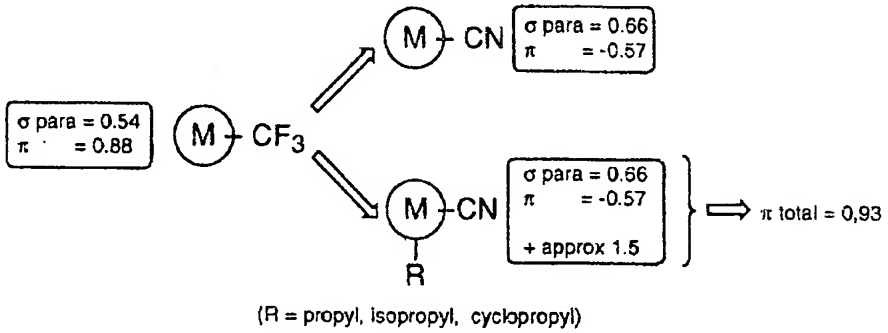


Fig. 13.23 The loss in lipophilicity resulting from the bioisosteric exchange of a CF_3 for a CN has to be compensated by the equivalent of a three-carbon residue.

IV. ANOMALIES IN ISOSTERISM

In this section, two applications of the bioisosterism concept that show unusual behaviours of commonly encountered atoms or groups are discussed.

A. Fluorine–hydrogen isosterism

There is an anomaly in the fact that fluorine does not resemble other halogens, notably chlorine, and that, on the other hand, it often mimics an atom of hydrogen.[88]

(a) Steric aspects. The fluorine atom is considerably smaller than the rest of the halogen atoms. Seen from the steric point of view, it resembles hydrogen more than chlorine (Table 13.10). Effectively fluoro derivatives differ from the other halogenated derivatives because with carbon fluorine forms particularly stable bonds and, in contrast to other halogens, is only rarely ionized or displaced. Because it is both chemically inert and of small size, organic fluorine is often compared to hydrogen.

This relates in particular to the incorporation by living organisms of fluoroacetic acid in place of acetic[89] acid or of 5-fluoronicotinic acid and 5-fluorouracil as antimetabolites (see Chapter 17, the section on halogens). This 'fraudulent' incorporation leads to lethal syntheses.[90] This is generally not the case with the corresponding chlorinated, brominated or iodinated analogues.

Table 13.10 Fluorine–hydrogen isosterism. Observe the comparable sizes of the two atoms, whereas chlorine is close to the methyl and trifluoromethyl.

Parameter	H	F	Cl	CH_3	CF_3
Atomic radius	0.29	0.64	0.99	-	-
Van der Waals radius	1.2	1.35	1.80	≈2	≈2
Molecular refractivity	1.03	0.92	6.03	5.65	5.02
Electronic effect (*para* σ)[a]	0.00	0.06	0.23	−0.17	0.54
Resonance effect (ℜ)[a]	0.00	−0.34	−0.15	−0.13	0.19
Electronic effect (σ*)[b]	–	3.08	2.68	0.00	2.85

[a]For aromatic systems, [b]for aliphatic systems

(b) Electronic aspects. Fluorine is the most electronegative of the halogens (Table 13.10) and forms particularly stable bonds with carbon atoms. This chemical inertia explains why fluoro derivatives are more resistant to metabolic degradation (Fig. 13.24). Thus for the β-haloalkylamines (nitrogen mustards), the alkylating activity is lost when chlorine or bromine are replaced by fluorine or by hydrogen.[91]

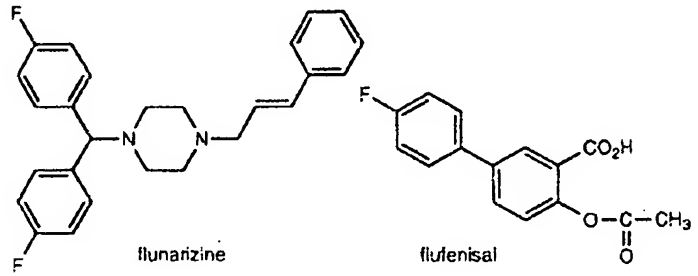


Fig. 13.24 In flunarizine and in flufenisal, fluorine atoms in *para* position prevent metabolic hydroxylation.

H ↔ F isosterism will therefore often serve to give analogues that are more resistant to metabolic degradation (obstructive halogenation: flunarizine and in flufenisal, Fig. 13.24). Similarly the CF_3 group is biostable, whereas CH_3 is easily oxidized.[88]

(c) Absence of d orbitals. Another difference between fluorine and the other halogens comes from the absence of a d orbital for fluorine, and thus its incapacity to participate in resonance effects with a donor of electrons p (Fig. 13.25). This explains why *p*-fluorophenol is slightly less acidic than phenol, while for other *p*-halogenated phenols the acidity changes in parallel with the atomic number (Table 13.11).[88]

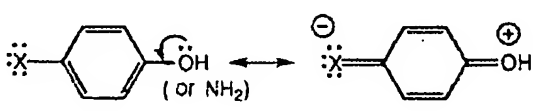
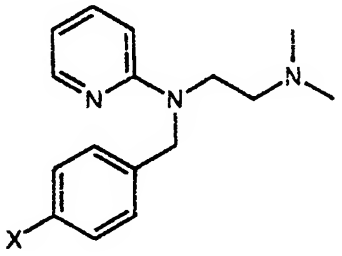


Fig. 13.25 The resonance betwen the OH lone pair and the X group is not possible if X = F.

Table 13.11 Dissociation constants of *para*-halogenated phenols.[88]

Compound	Dissociation constant $K_a \times 10^{-10}$
Phenol	0.32
p-Fluorophenol	0.26
p-Chlorophenol	1.32
p-Bromophenol	1.55
p-Iodophenol	2.19

(d) Case study. A good example of continous variation of activity in halogenated compounds is provided by a series of antihistaminic drugs related to tripelennamine (Fig. 13.26, X = H). Apparently we are dealing here with a classical isosteric series: F, Cl, Br, I, but sensitive to steric hindrance in the *para* position. Probably what happens *in vivo* is *p*-hydroxylation of the benzene ring. The best candidate becomes then the *p*-fluoro compound, since it is not bulkier than the unsubstituted compound while being biostable.

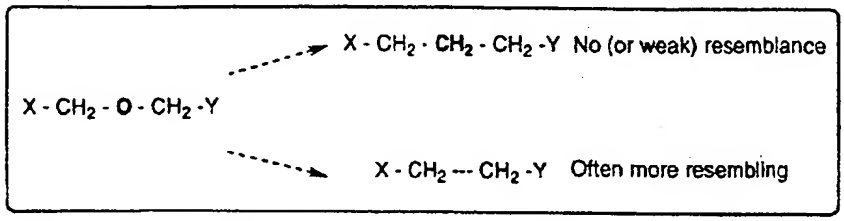


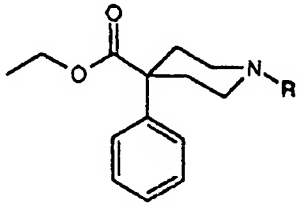
X	Activity
H	1
F	3-4
Cl	2-3
Br	1
I	0.3-0.5

Fig. 13.26 Variation of activity in a series of antihistaminic compounds as a function of the halogated *para*-substituent.[81]

B. Exchange of ether oxygen and methylene group

Ether oxygen atoms and methylene groups possess similar tetrahedral structure and should normally be isosteric. In fact the $O \leftrightarrow CH_2$ isosterism very often yields anomalous results and brought Friedman[2] to the interesting observation 'that the omission of the ether oxygen changes biological activity much less in some cases than the replacement by the isosteric methylene group' (Fig. 13.27). In the meperidine series, for example, the change from the *N*-phenoxypropyl derivative to the isosteric phenoxybutyl decreases the analgesic potency by a factor of 10, whereas the omission of the ether oxygen yields a slightly more potent compound.[10] A list of seven other examples is given by Schatz in the second edition of Burger's *Medicinal Chemistry*.[93]





R =	Analgesic Potency (meperidine = 1)
—(CH2)3—O—C6H5	15
—(CH2)3—CH2·C6H5	1.5
—(CH2)3— C6H5	20

Fig. 13.27 Friedman's ether oxygen–methylene group paradox.[2]

The explanation for this anomalous behaviour may be that the omission of the ether oxygen yields a closer compound in terms of lipophilicity than its replacement by a methylene. An example that can be compared to Friedman's paradox is found in the resemblance of the phenylethyl type β-blockers (e.g. dichloroisoprenaline, sotalol) to the phenoxypropanol type (e.g. practolol, acebutolol).

V. MINOR METALLOIDS — TOXIC ISOSTERES

In this section we describe some 'exotic' applications of the bioisostery concept involving the utilization of unusual elements such as silicon, boron and selenium.

A. Carbon–silicon bioisosterism

Silicon is directly below carbon in the periodic table and the incorporation of silicon in place of carbon in biologically active substances has been a temptation for many organic chemists. However, the extent of this isosterism remains limited. For reviews on the subject, see Fessenden and Fessenden,[94] Tacke and Zilch[95,96] and Ricci *et al.*[97]

Silicon is more electropositive than carbon (and even more so if compared to oxygen and nitrogen) and the covalent silicon–carbon bonds in the sp^3 hybridization state are 20% longer than the corresponding carbon–carbon bond. Compared to their carbon bioisosteres, silicon-containing molecules are more sensitive to hydrolysis and to nucleophilic attack in general. Given the chemical reactivity of silicon, carbon–silicon isosterism is generally practised only if the silicon is present in the centre of a quaternary structure, as is the case for substances collected in Fig. 13.28. Among these, *m*-trimethylsilylphenyl *N*-methylcarbamate and *m*-trimethylsilyl-α-trifluoroacetophenone (zifrosilone) are acetylcholinesterase inhibitors,[98–100] sila-meprobamate is a CNS depressant,[101] sila-pridinol is an anticholinergic,[102] flusilazole is a

fungicide for agricultural use,[103] and (+)-RP 71,602 is a potent and selective 5-HT_{2A} antagonist.[104]

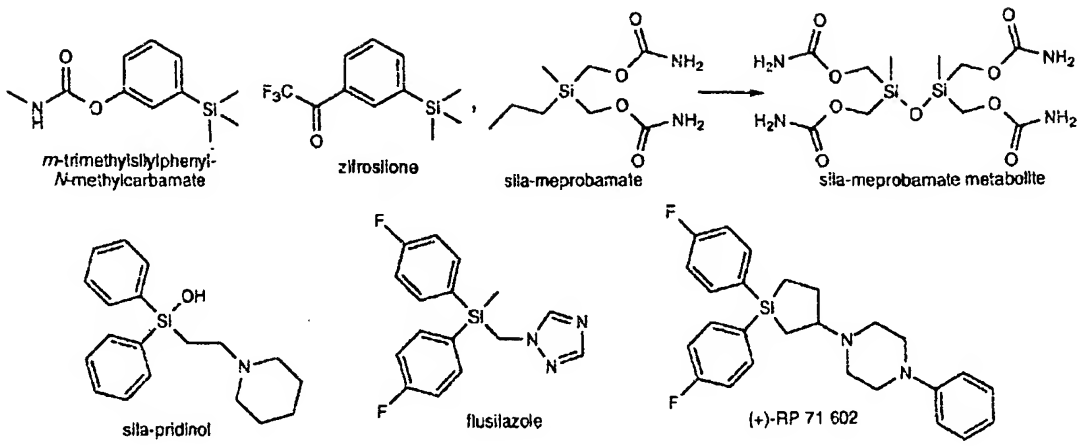


Fig. 13.28 Organosilicon active substances.

But even when located in the centre of a quaternary structure, the silicon atom can easily be attacked. Thus, 1-chloro-1-sila-bicyclo(2,2,1)heptane can still be hydrolysed by an attack on the vacant d orbital;[105] this attack is *lateral* and therefore possible even in the cases where the corresponding carbon derivative would have been inert towards S_N2 reaction (Fig. 13.29). This sensitivity towards lateral attacks explains the four times shorter duration of action of sila-meprobamate compared to its carbon isostere on a model of tranquillizing activity in mice (rotarod test, potentiation of hexobarbital-induced sleep; intraperitoneal injection).[101] On the other hand, when given orally, sila-meprobamate is practically inactive. One of the first metabolites formed has been characterized as being a disiloxane[106] (Fig. 13.28). For the two phenyltrimethylsilyl-derived AChE inhibitors, the rather positively charged trimethylsilyl group mimics the trimethylammonium function present in acetylcholine. For these compounds, metabolic oxidation does not take place on the silicon but on one of methyl groups ($Si-CH_3 \rightarrow Si-CH_2-OH$).[99]

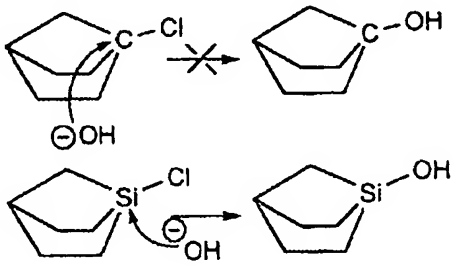


Fig. 13.29 Owing to the presence of a vacant d orbital, a lateral attack can substitute for dorsal attack in organosilicon derivatives.[94]

B. Carbon–boron isosterism

Organoboron derivatives, even more than organosilicon compounds, are sensitive to hydrolytic degradation that always leads to the final formation of boric acid. But boric acid has teratogenic properties in chickens. It produces the same malformations as those produced by a riboflavin (vitamin B_2) deficiency and the administration of riboflavin prevents these toxic effects.[107,108] The mechanism by which boric acid produces a deficiency in riboflavin is not known. In man the chronic utilization of boron derivatives results in cases of borism (dry skin, cutaneous eruptions, gastric troubles).[109]

Few medicines based on boron are known; in general boric acid or a boronic acid serve to esterify an α-diol or an *o*-diphenol. This is the case for the emetic antimony borotartrates of the ancient pharmacopoeias; for the injectable catecholamine solutions; for tolboxane,[110] which is close to meprobamate and was commercially available as a tranquillizer some decades ago; and also for the phenylboronic esters of chloramphenicol.[111] Boromycin was the first natural product containing boron. It is a complex between boric acid and a polyhydroxylated tetradentate macrocycle.[112] Some boronic analogues of amino acids were prepared as chymotrypsin and elastase inhibitors.[113] The most important medical use of derivatives of boron derivatives is the treatment of some tumours by neutron capture therapy,[114–116] the problem here being to ensure a sufficient concentration of the product in the tumour being treated.

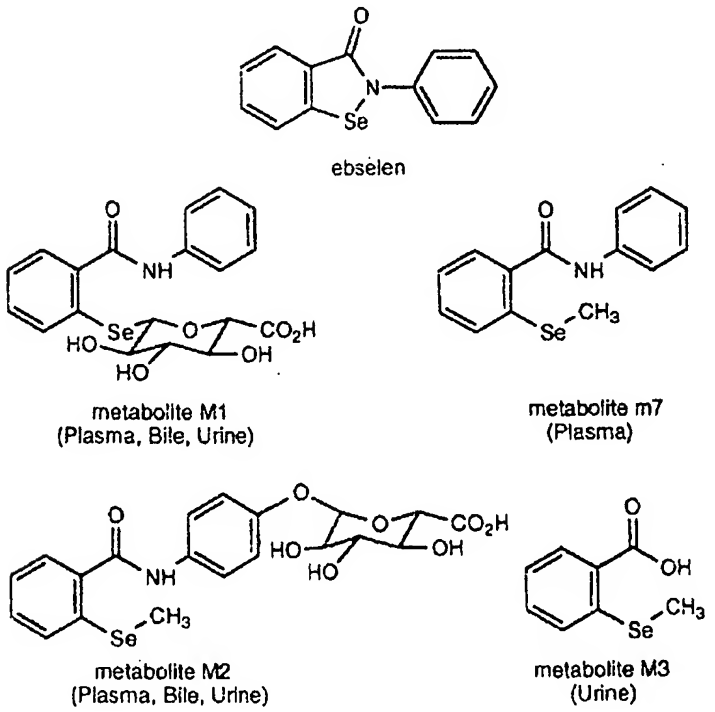


Fig. 13.30 Ebselen and its main metabolites.[119]

C. Bioisosterism involving selenium

Selenium and its derivatives are highly toxic and with the exception of ^{75}Se derivatives that serve diagnostic purposes (e.g. ^{75}Se-selenomethionine, used as a radioactive imaging agent in pancreatic scanning), there is no chemically defined seleno-organic drug on the market. Klayman reviewed a large number of selenium derivatives as chemotherapeutic agents in 1973.[117] Selenium bioisosteres of sulphur compounds are mainly used as research tools (e.g. bis(2-chloroethyl) selenide as selenium bioisostere of the classical sulphur mustards[118]). Selenocysteine is present in the catalytic site of mammalian glutathione peroxidase and this explains the importance of selenium as an essential trace element.

The only selenium-containing drug candidate is *ebselen* (Fig. 13.30), which owes its antioxidant and anti-inflammatory properties to its interference with the selenoenzyme glutathione peroxidase.[120] Because of its strongly bound selenium moiety, only metabolites of low toxicity are formed.[119]

REFERENCES

1. Langmuir, I. (1919) Isomorphism, isosterism and covalence. *J. Am. Chem. Soc.* **41**: 1543–1559.
2. Friedman, H. L. (1951) Influence of isosteric replacements upon biological activity. In *Symposium on Chemical-Biological Correlation.* National Research Council Publication, Washington D.C.
3. Grimm, H. G. (1925) Über Bau und Grösse der Nichtmetallhydride. *Z. Elektrochem.* **31**: 474–480.
4. Grimm, H. G. (1929) The system of chemical compounds from the viewpoint of atom research, several problems of experimental research. Part I. *Naturwissenschaften* **17**: 535–540.
5. Grimm, H. G. (1929) The system of chemical compounds from the viewpoint of atom research, several problems of experimental research. Part II. *Naturwissenschaften* **17**: 557–564.
6. Erlenmeyer, H. and Leo, M. (1932) Über Pseudoatome. *Helv. Chim. Acta* **15**: 1171–1186.
7. Erlenmeyer, H. (1948) Les composés isostères et le problème de la ressemblance en chimie. *Bull. Soc. Chim. Biol.* **30**: 792–805.
8. Thornber, C. W. (1979) Isosterism and molecular modification in drug design. *Chem. Soc. Rev.* **8**: 563–580.
9. Krogsgaard-Larsen, P., Hjeds, H., Falch, E., Jørgensen, F. S. and Nielsen, L. (1988) Recent advances in GABA agonists, antagonists and uptake inhibitors: structure–activity relationships and therapeutic potential. In Testa, B. (ed.) *Advances in Drug Research*, pp. 381–456. Academic Press, London.
10. Janssen, P. A. J. and Van der Eycken, C. A. M. (1968) The chemical anatomy of potent morphine-like analgesics. In Burger, A. (ed.) *Drugs Affecting the Central Nervous System*, pp. 25–60. Marcel Dekker, New York.
11. Boyle, E. A., Mangan, F. R., Markwell, R. E., Smith, S. A., Thompson, M. J., Ward, R. W. and Wyman, P. A. (1986) 7-Aroyl-2,3-dihydrobenzo[*b*]furan-3-carboxylic acids and 7-benzoyl-2,3-dihydrobenzo[*b*]thiophene-3-carboxylic acids as analgesic agents. *J. Med. Chem.* **29**: 894–898.
12. Chen, Y. L., Nielsen, J., Hedberg, K. D. A., Jones, S., Russo, L., Johnson, J., Ives, J. and Liston, D. (1992) Syntheses, resolution, and structure–activity relationships of potent acetylcholinesterase inhibitors: 898 carbaphysostigmine analogues. *J. Med. Chem.* **35**: 1429–1434.
13. Erlenmeyer, H. and Willi, E. (1935) Zusammenhänge zwischen Konstitution und Wirkung bei Pyrazolonderivaten. *Helv. Chim. Acta* **18**: 740–743.
14. Binder, D., Noe, C. R., Holzer, W. and Baumann, K. (1987) Thiophen als Strukturelement Physiologisch Aktiver Substanzen, 16. Thienoisoxazole Durch Substitution am Oximstickstoff. *Arch. Pharm.* **320**: 837–843.
15. Uno, H., Kurokawa, M., Masuda and Nishimura, H. (1979) Studies on 3-substituted 1,2-benzisoxazole derivatives. 6. Syntheses of 3-(sulfamoylmethyl)-1,2-benzisoxazole derivatives and their anticonvulsant activities. *J. Med. Chem.* **22**: 180–183.

16. Gold-Aubert, P., Melkonian, D. and Toribio, L. (1964) Synthèses de nouvelles phényl-1-triazoline-1,2,4-ones-5 substituées en 3 et 4. *Helv. Chim. Acta* **47**: 2068–2071.
17. Alonso, R., Andrès, J. I., Garcia-Lopez, M. -T., de las Heras, F. G., Herranz, R., Alarcòn, B. and Carrasco, L. (1985) Synthesis and antiviral evaluation of nucleosides of 5-methylimidazole-4-carboxamide. *J. Med. Chem.* **28**: 834–838.
18. Fludzinski, P., Evrard, D. A., Bloomquist, W. E. and Lacefield, W. B. (1987) Indazoles as indole bioisosteres: synthesis and evaluation of the tropanyl ester and amide of indazole-3-carboxylate as antagonists to the serotonin $5HT_3$ receptor. *J. Med. Chem.* **30**: 1535–1537.
19. Blaskó, G., Major, E., Blaskó, G., Rózsa, I. and Szántay, C. (1986) Pyrimido(1,6-*a*]pyrido(3,4-*b*] indoles as new platelet inhibiting agents. *Eur. J. Med. Chem.* **21**: 91–95.
20. Kardos, J., Blaskó, G., Simonyi, M. and Szántay, C. (1985) Octahydroindolo[2,3-a]quinolizin-2-one, a novel structure for γ-aminobutyric acid (GABA) uptake inhibition. *Eur. J. Med. Chem.* **21**: 151–154.
21. Salituro, F. G., Harrison, B. L., Baron, B. M., Nyce, P. L., Stewart, K. T., Kehne, J. H., White, H. S. and McDonald, I. (1992) 3-(2-Carboxyindol-3-yl)propionic acid-based antagonists of the *N*-methyl-D-aspartic receptor associated glycine binding site. *J. Med. Chem.* **35**: 1791–1799.
22. Calvino, R., Stilo, A. D., Fruttero, R., Gasco, A. M., Sorba, G. and Gasco, A. (1993) Pharmacochemistry of the furoxan ring: recent developments. *Il Farmaco* **48**: 321–334.
23. Lipinski, C. A., Aldinger, C. E., Beyer, T. A., Bordner, J., Burdi, D. F., Bussolotti, D. L., Inskeep, P. B. and Siegel, T. W. (1992) Hydantoin isosteres. *In vivo* active spiro hydroxy acetic aldose reductase inhibitors. *J. Med. Chem.* **35**: 2169–2177.
24. Ganellin, C. R. (1993) Discovery of cimetidine, ranitidine and other H_2-receptor histamine antagonists. In Ganellin, C. R. and Roberts, S. M. (eds) *Medicinal Chemistry — The Role of Organic Chemistry in Drug Research*, pp. 227–255. Academic Press, London.
25. Morin, I. (1991) 3-Aryl as-triazines: bioisostérie avec les 6-aryl pyridazines 1991. PhD thesis, Université Louis Pasteur, Strasbourg.
26. Mallamo, J. P., Pilling, G. M., Wetzel, J. R., Kowalczik, P. J., Bell, M. R., Kullnig, R. K., Batzold, F. H., Juniewiecz, P. E., Winnecker, R. C. and Luss, H. R. (1992) Antiandrogenic steroidal sulfonyl heterocycles. Utility of electrostatic complementarity in defining bioisosteric sulfonyl heterocycles. *J. Med. Chem.* **35**: 1663–1670.
27. Almquist, R. G., Chao, W. R. and Jennings-White, C. (1985) Synthesis and biological activity of carboxylic acid replacement analogues of the potent angiotensin converting enzyme inhibitor 5(S)-benzamido-4-oxo-6-phenylhexanoyl-L-proline. *J. Med. Chem.* **28**: 1067–1071.
28. Kohler, H. V., Eichler, B. and Salewski, R. (1970) Untersuchungen zum sauerstoffanalogen Charakter der $C(CN)_2$ -und NCN-gruppen. *Z. Anorg. Chem.* **379**: 183–192.
29. Bovy, P. R., Reitz, D. B., Collins, J. T., Chamberlain, T. S., Olins, G. M., Corpus, V. M., McMahon, E. G., Palomo, M. A., Koepke, J. P., McGraw, D. E. and Gaw, G. J. (1993) Nonpeptide angiotensin II antagonists: *N*-phenyl-1-*H*-pyrrole derivatives are angiotensin II receptor antagonists. *J. Med. Chem.* **36**: 101–110.
30. Marshall, W. S., Goodson, T., Cullinan, G. J., Swanson-Bean, D., Haisch, K. D., Rinkema, L. E. and Fleisch, J. H. (1987) Leukotriene receptor antagonists. I. Synthesis and structure–activity relationships of alkoxyacetophenone derivatives. *J. Med. Chem.* **30**: 682–689.
31. Krogsgaard-Larsen, P. (1990) In Hansch, C., Sammes, P. G., Taylor, J. B. and Emmet, J. C. (eds), *Comprehensive Medicinal Chemistry*, pp. 493–537. Pergamon Press, Oxford.
32. Lunn, W. H. W., Schoepp, D. D., Lodge, D., True, R. A. and Millar, J. D. (1992) LY262466, DL-2-amino-3-(4-hydroxy-1,2,5-thiazol-3-yl) propanoic acid hydrochloride, a novel and selective agonist at the AMPA excitatory amino acid receptor. In *XIIth International Symposium on Medicinal Chemistry*. Basel, Switzerland, September 13–17.
33. Atkinson, J. G., Girard, Y., Rokach, J., Rooney, C. S., McFarlane, C. S., Rackham, A. and Share, N. N. (1979) Kojic amine-A novel γ-aminobutyric acid analogue. *J. Med. Chem.* **22**:90–106.
34. Froestl, W., Furet, P., Hall, R. G., Mickel, S. J., Strub, D., Sprecher, G. v., Baumann, P. A., Bernasconi, R., Brugger, F., Felner, A., Gentsch, C., Hauser, K., Jaeckel, J., Karlsson, G., Klebs, K., Maître, L., Marescaux, C., Moser, P., Pozza, M. F. and Rihs, G. (1993) $GABA_B$ antagonists: novel CNS-active compounds. In Testa, B., Kyburz, E., Fuhrer, W. and Giger, R. (eds) *Perspectives in Medicinal Chemistry*, pp. 259–272. VHC, Weinheim.
35. Drummond, J. T. and Johnson, G. (1988) Convenient procedure for the preparation of alkyl end aryl substituted N-(aminoalkylacyl)sulfonamides. *Tetrahedron Lett.* **29**: 1653–1656.

36. Albright, J. D., DeVries, V. G., Du, M. D., Largis, E. E., Miner, T. G., Reich, M. F. and Shepherd, R. G. (1983) Potential antiatherosclerotic agents. 3. Substituted benzoic and non benzoic analogues of cetabon. *J. Med. Chem.* **26**: 1393–1411.
37. Buu-Hoï, N. P., Lambelin, G., Lepoivre, C., Gillet, C., Gautier, M. and Thiriaux, J. (1965) Un nouvel agent antiinflammatoire de structure non stéroïdique: l'acide p-butoxyphénylacéthydroxamique. *C. R. Acad. Sci. (Paris)* **261**: 2259–2262.
38. Orzalesi, G. and Selleri, R. (1974) Pharmaceutical 2-(4-isobutylphenyl) propionohydroxamic acid. German Patent 2 400 531 (24 July 1974; to Societa Italo-Britannica L. Manetti & H. Roberts e C.) *Chem. Abstr.* **81**: 120272i.
39. De Martiis, F., Corsico, N., Franzone, J. S. and Tamietto, T. (1975) Valutazione farmaco-tossicologica di un nuovo agente antifiammatorio non steroideo: l'acido indoxamico. *Boll. Chim. Farm.* **114**: 319–333.
40. Summers, J. B., Masdiyasni, H., Holms, J. H., Ratajczik, J. D., Dyer, R. D. and Carter, G. W. (1987) Hydroxamic acid inhibitors of 5-lipoxygenase. *J. Med. Chem.* **30**: 574–580.
41. Bergeron, R. J., Liu, Z. -R., McManis, J. S. and Wiegand, J. (1992) Structural alterations in desferioxamine compatible with iron clearance in animals. *J. Med. Chem.* **35**: 4739–4744.
42. Kwon, C. -H., Nagasawa, H. T., DeMaster, E. G. and Shirota, F. N. (1986) Acyl, N-protected α-aminoacyl, and peptidyl derivatives as prodrug forms of the alcohol deterrent agent cyanamide. *J. Med. Chem.* **29**: 1922–1929.
43. De Martiis, F., Franzone, J. S. and Tamietto, T. (1975) Sintesi e proprieta antiflogistiche di alcuni acidici indolil-acetoidrossammici. *Bol. Chim. Farm.* **114**: 309–318.
44. Orzalesi, G., Mari, F., Bertol, E., Selleri, R. and Pisaturo, G. (1980) Anti-inflammatory agents: determination of ibuproxam and its metabolite in humans. *Arzneim.-Forsch.* **30**: 1607–1609.
45. Demay, F. and De Sy, J. (1982) A new non-steroidal anti-inflammatory drug (NSAID) in current rheumatologic practice (oxamethacin). *Curr. Ther. Res.* **31**: 113–118.
46. Vergin, H. v., Ferber, H., Brunner, F. and Kukovetz, W. R. (1981) Pharmakokinetik und Biotransformation von Oxametacin bei gesunden Probanden. *Arzneim.-Forsch* **31**: 513–518.
47. Singh, H., Chawla, A. S., Kapoor, V. K., Paul, D. and Malhotra, R. K. (1980) Medicinal chemistry of tetrazoles. In Ellis, G. P. and West, G. B. (eds) *Progress in Medicinal Chemistry*, pp. 151–183. Elsevier, Amsterdam.
48. Ashton, W. T., Cantone, C. L., Chang, L. L., Hutchins, S. M., Strelitz, R., MacCross, M., Chang, R. S. L., Lotti, V. J., Faust, K. A., Chen, T. -B., Bunting, P., Schorn, T. W., Sivlighn, S. D. and Siegl, P. K. S. (1993) Nonpeptide angiotensin II antagonists derived from 4*H*-1,2,4-triazoles and 3*H*-imidazo[1,2-*b*][1,2,4]triazoles. *J. Med. Chem.* **36**: 591–609.
49. Marshall, W. S., Goodson, T., Cullinan, G. J., Swanson-Bean, D., Haisch, K. D., Rinkema, L. E. and Fleisch, J. H. (1987) Leukotriene receptor antagonists. 1. Synthesis and structure–activity relationships of alkoxyacetophenone derivatives. *J. Med. Chem.* **30**: 682–689.
50. Kraus, J. L. (1983) Isosterism and molecular modification in drug design: tetrazole analogue of GABA: Effects on enzymes of the gamma-aminobutyrate system. *Pharmacol. Res. Commun.* **15**: 183–189.
51. Schlewer, G., Wermuth, C. G. and Chambon, J. -P. (1984) Analogues tétrazoliques d'agents GABA-mimétiques. *Eur. J. Med. Chem.* **19**: 181–186.
52. Krogsgaard-Larsen, P., Rodolskov-Christiansen, T. (1979) GABA agonists. Synthesis and structure–activity studies on analogues of isoguvacine and THIP. *Eur. J. Med. Chem.* **14**: 157–164.
53. Krogsgaard-Larsen, P. (1981) γ-Aminobutyric acid agonists, antagonists, and uptake inhibitors. Design and therapeutic aspects. *J. Med. Chem.* **24**: 1377–1383.
54. Krogsgaard-Larsen, P., Ferkany, J. W., Nielsen, E. O., Madsen, U., Ebert, B., Johansen, J. S., Diemer, S. H., Bruhn, T., Beattie, D. T. and Curtis, D. R. (1991) Novel class of amino acid antagonists at non-*N*-methyl-D-aspartic acid excitatory amino acid receptors. Synthesis, *in vitro* and *in vivo* pharmacology, and neuroprotection. *J. Med. Chem.* **34**: 123–130.
55. Kraus, J. L. (1983) Isosterism and molecular modification in drug design: new n-dipropylacetate analogs as inhibitors of succinic semi aldehyde dehydrogenase. *Pharmacol. Res. Commun.* **15**: 119–129.
56. Lichtenthaler, F. W. and Heidel, P. (1969) Intermediates in the formation of γ-pyrones from hexose derivatives: a simple synthesis of kojic acid and hydroxymaltol. *Angew. Chem. Int. Ed.* **8**: 978–979.

57. Watkins, J. C., Krogsgaard-Larsen, P. and Honoré, T. (1990) Structure–activity relationships in the development of excitatory amino acid receptor agonists and competitive antagonists. *Trends Pharm. Sci.* **11**: 25–33.
58. Drysdale, M. J., Pritchard, M. C. and Horwell, D. C. (1992) Rationally designed 'dipeptoid' analogues of CCK. Acid mimics of the potent and selective non peptide CCK-B receptor antagonist CI-988. *J. Med. Chem.* **35**: 2573–2581.
59. Kinney, W. A., Lee, N. E., Garrison, D. T., Podlesny, Jr., E. J., Simmonds, J. T., Bramlet, D., Notvest, R. R., Kowal, D. M. and Tasse, R. P. (1992) Bioisosteric replacement of the α-amino carboxylic functionality in 2-amino-5-phosphonopentanoic acid yields unique 3,4-diamino-3-cyclobutene-1,2-dione containing NMDA antagonists. *J. Med. Chem.* **35**: 4720–4726.
60. Shapiro, G., Floersheim, P. Boelsterli, J., Amstutz, R., Bolliger, G., Gammenthaler, H., Gmelin, G., Supavilai, P. and Walkinshaw, M. (1992) Muscarinic activity of the thiolactone, lactam, lactol, and thiolactol analogues of pilocarpine and a hypothetical model for the binding of agonists to the m_1 receptor. *J. Med. Chem.* **35**: 15–27.
61. Thompkins, L. and Lee, K. H. (1975) Comparison of analgesic effects of isosteric variations of salicylic acid and aspirin (acetylsalicylic acid). *J. Pharm. Sci.* **64**: 760–763.
62. Roth, G. J., Stanford, N., Majerus, P. W. (1975) Acetylation of prostaglandine synthase by aspirin. *Proc. Nat. Acad. Sci., USA* **72**: 3073–3076.
63. Saunders, J., Cassidy, M., Freedman, S. B., Harley, E. A., Iversen, L. L., Kneen, C., MacLeod, A. M., Merchant, K., Snow, R. J. and Baker, R. (1990) Novel quinuclidine-based ligands for the muscarinic cholinergic receptor. *J. Med. Chem.* **33**: 1128–1138.
64. Sauerberg, P., Kindtler, J. W., Nielsen, L., Sheardown, M. J. and Honoré, T. (1991) Muscarinic cholinergic agonists and antagonists of the 3-(3-alkyl-1,2,4-oxadiazol-5-yl)-1,2,5,6-tetrahydropyridine type. Synthesis and structure–activity relationships. *J. Med. Chem.* **34**: 687–692.
65. Sauerberg, P., Olesen, P. H., Nielsen, S., Treppendahl, S. M. J. S., Honoré, T., Mitch, C. H., Ward, J. S., Pike, A. J., Bymaster, F. P., Sawyer, B. D. and Shannon, H. E. (1992) Novel functional M_1 selective muscarinic agonists. Synthesis and structure–activity relationships of 3-(1,2,5-thiadiazolyl)-1,2,5,6-tetrahydro-1-methylpyridines. *J. Med. Chem.* **35**: 2274–2263.
66. Wadsworth, H. J., Jenkins, S. M., Orlek, B. S., Cassidy, F., Clark, M. S. G., Brown, F., Riley, G. J., Graves, D., Hawkins, J. and Naylor, C. (1992) Synthesis and muscarinic activities of quinuclidin-3-yltriazole and -tetrazole derivatives. *J. Med. Chem.* **35**: 1280–1290.
67. Street, L. J., Baker, R., Book, T., Reeve, A. J., Saunders, J., Willson, T., Marwood, R. S., Patel, S. and Freedman, S. B. (1992) Synthesis and muscarinic activity of quinuclidinyl- and (1-azanorbornyl)pyrazine derivatives. *J. Med. Chem.* **35**: 295–305.
68. Kozikowski, A. P., Roberti, M., Xiang, L., Bergmann, J. S., Callahan, P. M., Cunningham, K. A. and Johnson, K. M. (1993) Structure–activity relationship studies of cocaine: replacement of the C-2 ester group by vinyl argues against H-bonding and provides an esterase-resistant, high-affinity cocaine analogue. *J. Med. Chem.* **35**: 4764–4766.
69. Lipinski, C. A. (1986) Bioisosterism in drug design. In Bailey, D. M. (ed.) *Anual Reports in Medicinal Chemistry*, pp. 283–291. Academic Press, San Diego.
70. Wermuth, C. G. (1993) Aminopyridazines — an alternate route to potent muscarinic agonists with no cholinergic syndrome. *Il Farmaco* **48**: 253–274.
71. Huff, J. R., Anderson, P. S., Baldwin, J. J., Clineschmidt, B. V., Guare, J. P., Lotti, V. J., Pettibone, D. J., Randall, W. C. and Vacca, J. P. (1985) *N*-(1,3,4,6,7,12b-hexahydro-2*H*-benzo[b]furo[2,3-a]quinolizin-2-yl)-*N*-methyl-2-hydroxyethane-sulfonamide: a potent and selective α_2-adrenoreceptor antagonist. *J. Med. Chem.* **28**: 1756–1759.
72. Fournier, J. -P., Moreau, R. C., Narcisse, G. and Choay, P. (1982) Synthèse et propriétés pharmacologiques de sulfonylurées isostères du glibenclamide. *Eur. J. Med. Chem.* **17**: 81–84.
73. Spatola, A. F. (1983) Peptide backbone modifications: structure–activity analysis of peptides containing amide bond surrogates. In Weinstein, B. (ed.) *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins*, pp. 267–357. Marcel Dekker, New York.
74. Fauchère, J. -L. (1986) Elements for the rational design of peptide drugs. In Testa, B. (ed.) *Advances in Drug Research*, pp. 29–69. Academic Press, London.
75. Smith III, A. B., Holcomb, R. C., Guzman, M. C., Keenan, T. P., Sprengeler, P. A. and Hirschmann, R. (1993) An effective synthesis of scalemic 3,5,5-trisubstituted pyrrolin-4-ones. *Tetrahedron Lett.* **34**: 63–66.

76. Smith III, A. B., Keenan, T. P., Holcomb, R. C., Sprengeler, P. A., Guzman, M. C., Wood, J. L., Carroll, P. J. and Hirschmann, R. (1992) Design, synthesis and crystal structure of a pyrrolinone-based peptidomimetic possessing the conformation of a β-strand: potential application to the design of novel inhibitors of proteolytic enzymes. *J. Amer. Chem. Soc.* **114**: 10672–10674.
77. Allmendinger, T., Felder, E. and Hungerbuehler, E. (1991) Fluoroolefin dipeptide isosteres. In Weldi, J. T. (ed.) *Selective Fluorination in Organic and Bioorganic Chemistry*, pp. 186–195. American Chemical Society, Washington.
78. Chandrakumar, N. S., Yonan, P. K., Stapelfeld, A., Svage, M., Rorbacher, E., Contreras, P. C. and Hammond, D. (1992) Preparation and opioid activity of analogues of the analgesis dipeptide 2,6-dimethyl-l-tyrosyl-*N*-(3-phenylpropyl)-D-alanylamide. *J. Med. Chem.* **35**: 223–233.
79. Yanagisawa, I., Hirata, Y. and Ishii, Y. (1984) Histamine H_2 receptor antagonists. 1. Synthesis of *N*-cyano and *N*-carbamoyl amidine derivatives and their biological activities. *J. Med. Chem.* **27**: 849–857.
80. Young, R. C., Durant, G. J., Emmet, J. C., Ganellin, C. R., Graham, M. J., Mitchell, R. C., Prain, H. D. and Roantree, M. L. (1986) Dipole moment in relation to H_2 receptor antagonist activity for cimetidine analogues. *J. Med. Chem.* **29**: 44–49.
81. Lumma Jr, W. C., Anderson, P. S., Baldwin, J. J., Bolhofer, W. A., Habecker, C. N., Hirshfield, J. M., Pietruszkewicz, A. M., Randall, W. C., Torchiana, M. L., Britcher, S. F., Clineschmidt, B. V., Denny, G. H., Hirschmann, R., Hoffman, J. M., Phillips, B. T. and Streeter, K. B. (1982) Inhibitors of gastric acid secretion: 3,4-diamino-1,2,5-thiadiazole 1-oxides and 1,1-dioxides as urea equivalents in a series of histamine H_2-receptor antagonists. *J. Med. Chem.* **25**: 207–210.
82. Young, R. C., Ganellin, C. R., Graham, M. J. and Grant, E. H. (1982) The dipole moments of 1,3-dimethylthiourea, 1,3-dimethyl-2-cyanoguanidine and 1,1-bis-methylamino-2-nitroethene in aqueous solution. *Tetrahedron* **38**: 1493–1497.
83. Young, R. C., Ganellin, C. R., Graham, M. J., Roantree, M. J. and Grant, E. H. (1985) The dielectric properties of seven polar amidine-containing compounds of biological interest. *Tetrahedron Lett.* **26**: 1897–1900.
84. Plattner, J. J. and Norbeck, D. W. (1990) Obstacles to drug development from peptide leads. In Clark, C. R. and Moos, W. H. (eds) *Drug Discovery Technologies*, pp. 92–126. Ellis Horwood Limited, New York.
85. Büchi, J., Stünzi, E., Flury, M., Hirt, R., Labhart, P. and Ragaz, L. (1951) Über lokalanästhetisch wirksame basische Ester und Amide verschiedener Alkoxy-amino-benzoesäuren. *Helv. Chim. Acta* **34**: 1002–1013.
86. Wilhelm, M. (1975) The chemistry of polycyclic psycho-active drugs: serendipity or systematic investigation? *Pharm. J.* **214**: 414–416.
87. Larson, A. A. and Lish, P. M. (1964) A new bio-isostere: alkylsulphonamido-phenethanolamines. *Nature (London)* **203**: 1283–1285.
88. Chenoweth, M. B. and McCarthy, L. P. (1963) On the mechanism of the pharmacophoric effect of halogenation. *Pharmacol. Rev.* **15**: 673–707.
89. Goldman, P. (1969) The carbon–florine bond in compounds of biological interest. *Science* **164**: 1123–1130.
90. Peters, R. A. (1963) *Biochemical Lesions and Lethal Synthesis.* Pergamon Press, Oxford.
91. Chapman, N. B., James, J. W., Graham, J. D. P. and Lewis, G. P. (1952) Chemical reactivity and pharmacological activity among 2-haloethylamine derivatives with a naphtylmethyl group. *Chem. Ind. (London)* 805–807.
92. Vaughan, J. R. J., Anderson, G. W., Clapp, R. C., Clark, J. H., English, J. P., Howard, K. L., Marson, H. W., Sutherland, L. H. and Denton, J. J. (1949) Antihistamine agents. IV. Halogenated N,N-dimethyl-N′-benzyl-N-(2-pyridyl)-ethylenediamines. *J. Org. Chem.* **14**: 228–234.
93. Schatz, V. B. (1963) Isosterism and bioisosterism. In Burger, A. (ed.) *Medicinal Chemistry*, pp. 72–88. Interscience Publishers, Inc., New York.
94. Fessenden, R. J. and Fessenden, J. S. (1967) The biological properties of silicon compounds. In Harper, N. J. and Simmonds, A. B. (eds), *Advances in Drug Research*, pp. 95–132. Academic Press, London.
95. Tacke, R. and Zilch, H. (1986) Drug-design by sila-substitution and microbial transformations of organosilicon compounds: some recent results. *L'Actualité Chimique*, 75–82.
96. Tacke, R. and Zilch, H. (1986) Sila-substitution — a useful strategy for drug design? *Endeavour, New Series* **10**: 191–197.

97. Ricci, A., Seconi, G. and Taddei, M. (1989) Bioorganosilicon chemistry: trends and perspectives. *Chimica Oggi-Chemistry Today* **7**: 15–21.
98. Metcalf, R. L. and Fukuto, T. R. (1965) Silicon-containing carbamate insecticides. *J. Econ. Entomol.* **58**: 1151.
99. Anonymous Zifrosilone. *Drugs Fut.* **19**: 854–855.
100. Hornsperger, J. -M., Collard, N. -N., Heydt, J. G., Giacobini, E., Funes, S., Dow, J. and Schirlin, D. (1994) Trimethysilylated trifluoromethyl ketones, a novel class of acetylcholinesterase inhibitors: biochemical and pharmacological profile of MDL 73,745. *Biochem. Soc. Transactions* **22**: 758–763.
101. Fessendon, R. J. and Coon, M. D. (1965) Silicon-substituted medicinal agents. Silacarbamates related to meprobamate. *J. Med. Chem.* **8**: 604–608.
102. Tacke, R. (1980) Sila-pharmaka, XIX. Sila-pridinol und Pridinol: Darstellung und Eigenschaften sowie Strukturen im kristallinen und gelösten Zustand. *Chem. Ber.* **113**: 1962–1980.
103. Moberg, W. K. (1985) Synthesis of flusilazole. US patent 4 510 136 to DuPont.
104. Damour, D. M. B., Dutruc-Rosset, G., Doble, A., Piot, O. and Mignani, S. (1994) 1,1-Diphenyl-3-dialkylamino-1-silacyclopentane derivatives: a new class of potent and selective 5-HT_{2A} antagonists. *Bioorg. Med. Chem. Lett.* **4**: 415–420.
105. Sommer, L. H., Bennet, O. F., Campbell, P. G. and Weyenberg, D. R. (1957) Stereochemistry of hydride ion displacement from silicon. Enhanced rates at bridgehead and 4-ring silicon atoms. *J. Am. Chem. Soc.* **79**: 3295–3296.
106. Fessenden, R. J. and Ahlfors, C. (1967) The metabolic fate of some silicon-containing carbamates. *J. Med. Chem.* **10**: 810–812.
107. Landauer, W. (1954) On the chemical production of developmental abnormalities and of phenocopies in chicken embryos. *J. Cell. Comp. Physiol.* **43**(1): 261–305.
108. Landauer, W. and Clark, E. M. (1964) On the role of riboflavin in the teratogenic activity of boric acid. *J. Exptl. Zool.* **156**: 307–312.
109. Browning, E. (1969) *Toxicity of Industrial Metals.* Second Edition ed., pp. 90–97. Appleton-Century-Crofts, New York.
110. Caujolle, Pham-Huu-Chan (1968) Structure chimique et activité spasmolytique des organoboriques. *Arch. Int. Pharmacodyn. Ther.* **172**: 467–474.
111. Mubarak, S. I. M., Stanford, J. B. and Sugden, J. K. (1984) Some aspects of the antimicrobial and chemical properties of phenyl boronate esters of chloramphenicol. *Drug Dev. Ind. Pharm.* **10**: 1131–1160.
112. Dünitz, J. D., Hawley, D. M., Miklos, D., White, D. N. J., Berlin, Y., Marusik, R. and Prelog, V. (1971) Structure of boromycin. *Helv. Chim. Acta* **54**: 1709–1713.
113. Kinder, D. H. and Katzenellenbogen, J. A. (1985) Acylamino boronic acids and difluoroborane analogues of amino acids: potent inhibitors of chymotrypsine and elastase. *J. Med. Chem.* **28**: 1917–1925.
114. Alam, F., Soloway, A. H., Bapat, B. V., Barth, R. F. and Adams, D. M. (1989) Boron compounds for neutron capture therapy. *Basic Life Sci.* **50**: 107–111.
115. Kahl, S. B., Joel, D. D., Finkel, G. C., Micca, P. L., Nawrocky, M. M. and Coderre, J. A. (1989) A carboranyl porphyrin for boron neutron capture therapy of brain tumours. *Basic Life Sci.* **50**: 193–203.
116. Gabel, D. (1989) Tumor-seeking for boron neutron capture therapy: synthesis and biodistribution. *Basic Life Sci.* **50**: 233–241.
117. Klayman, D. L., Günther, W. H. H. (1973) *Organic Selenium Compounds: Their Chemistry and Biology.* Wiley-Interscience, New York.
118. Kang, S.-I. and Spears, C. P. (1987) Linear free energy relationships and cytotoxicities of para-substituted 2-haloethyl aryl selenides and bis(-chloroethyl) selenides. *J. Med. Chem.* **30**: 597–602.
119. Fischer, H., Terlinden, R., Löhr, J. P. and Römer, A. (1988) A novel biologically active selenoorganic compound. VIII. Biotransformation of ebselen. *Xenobiotica* **18**: 1347–1359.
120. Parnham, M. J. and Graf, E. (1987) Seleno-organic compounds and the therapy of hydroperoxide-linked pathological conditions. *Biochem. Pharmacol.* **36**: 3095–3102.